US011628162B2

(12) **United States Patent**
Ji et al.

(10) **Patent No.: US 11,628,162 B2**
(45) **Date of Patent: Apr. 18, 2023**

(54) **METHODS OF TREATING CANCER WITH AN FGFR INHIBITOR**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 177 days.

(21) Appl. No.: **16/811,640**

(22) Filed: **Mar. 6, 2020**

(65) **Prior Publication Data**

US 2020/0281907 A1 Sep. 10, 2020

Related U.S. Application Data

(60) Provisional application No. 62/815,772, filed on Mar. 8, 2019.

(51) **Int. Cl.**

A61K 31/4375	(2006.01)
A61K 31/5375	(2006.01)
A61K 31/5377	(2006.01)
A61P 35/00	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/4375*** (2013.01); ***A61K 31/5375*** (2013.01); ***A61K 31/5377*** (2013.01); *A61P 35/00* (2018.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

This application relates to methods of treating cancer in a patient in need thereof, comprising administering a Fibroblast Growth Factor Receptors (FGFR) inhibitor to the patient.

11 Claims, 10 Drawing Sheets

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FIG. 1

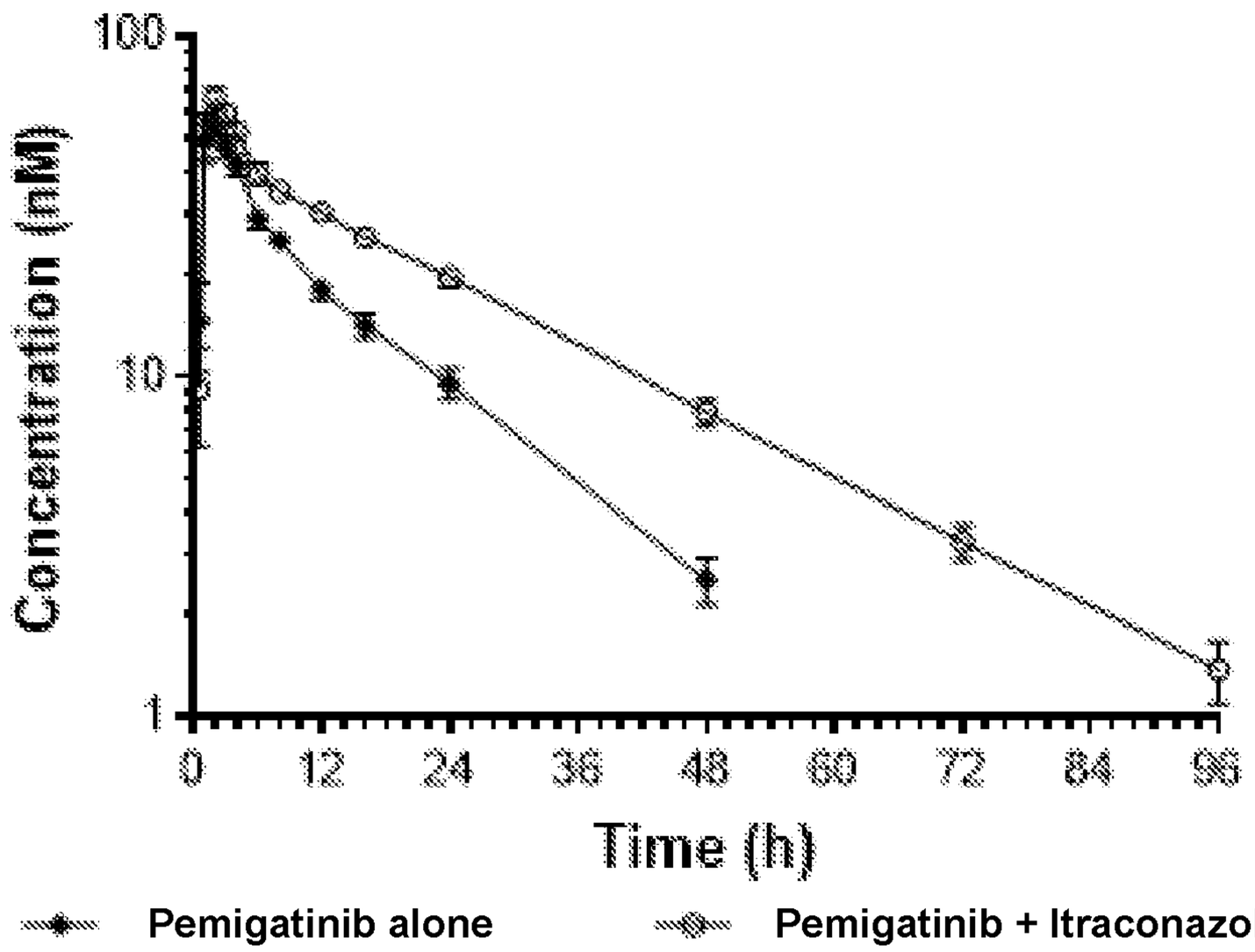

100
10
1
Concentration (nM)
0
12
24
36
48
60
72
84
96
Time (h)
Pemigatinib alone
Pemigatinib + Itraconazole

FIG. 2

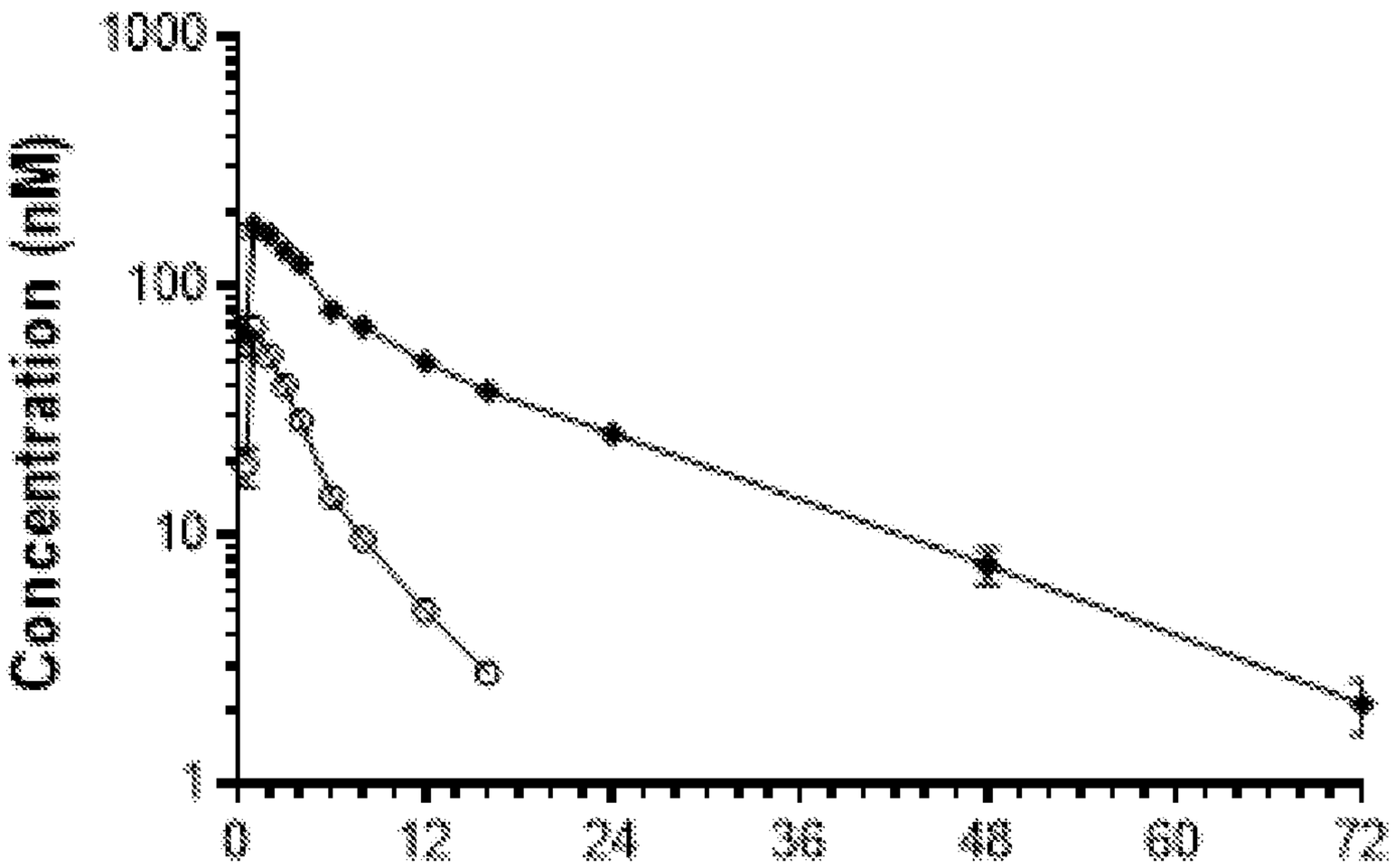

1000
100
10
1
Concentration (nM)
0
12
24
36
48
60
72
Time (h)
Pemigatinib alone
Pemigatinib + Rifampin

FIG. 3A

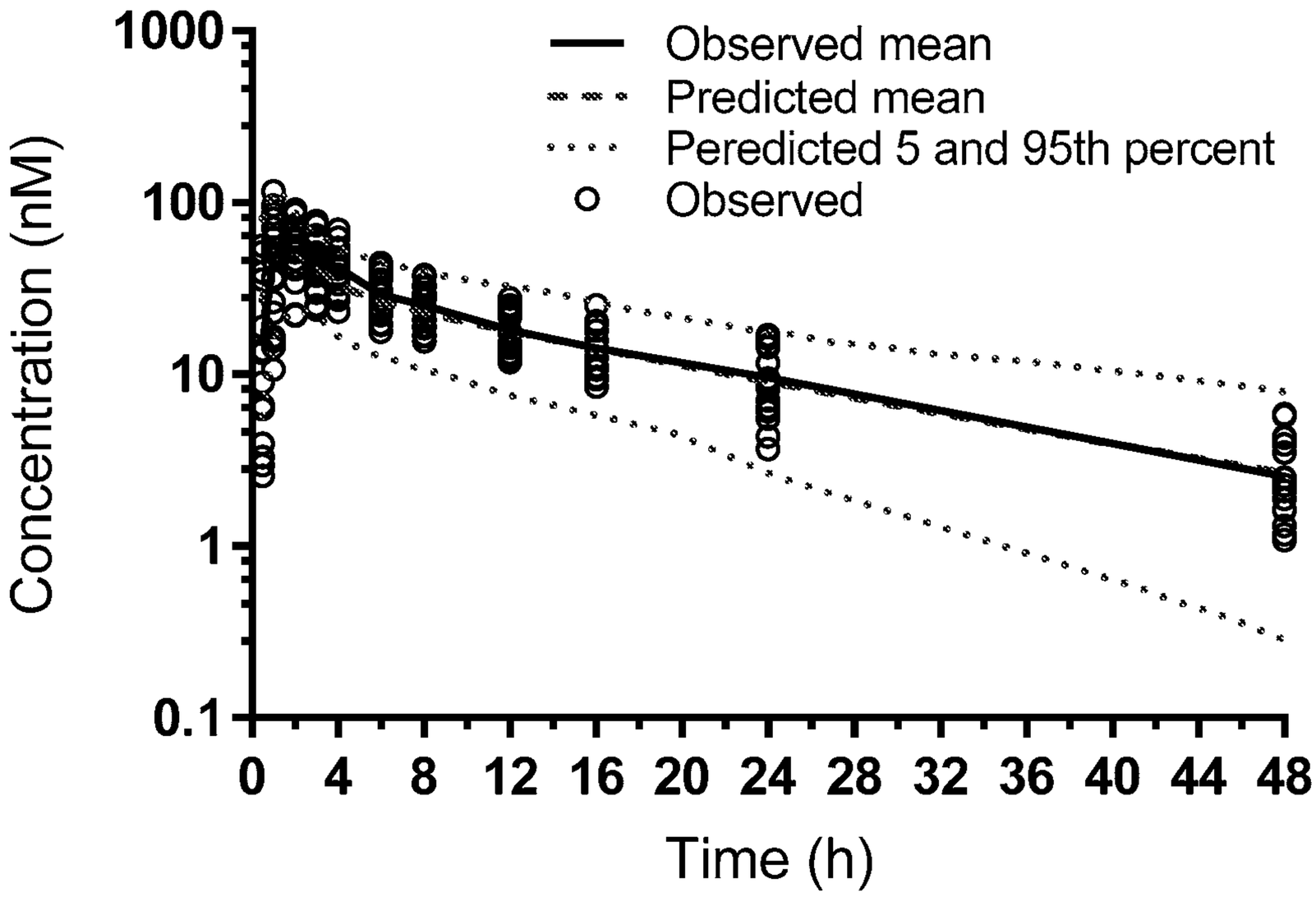

Observed mean
Predicted mean
Peredicted 5 and 95th percent
Observed
Concentration (nM)
1000
100
10
1
0.1
0
4
8
12
16
20
24
28
32
36
40
44
48
Time (h)

FIG. 3B

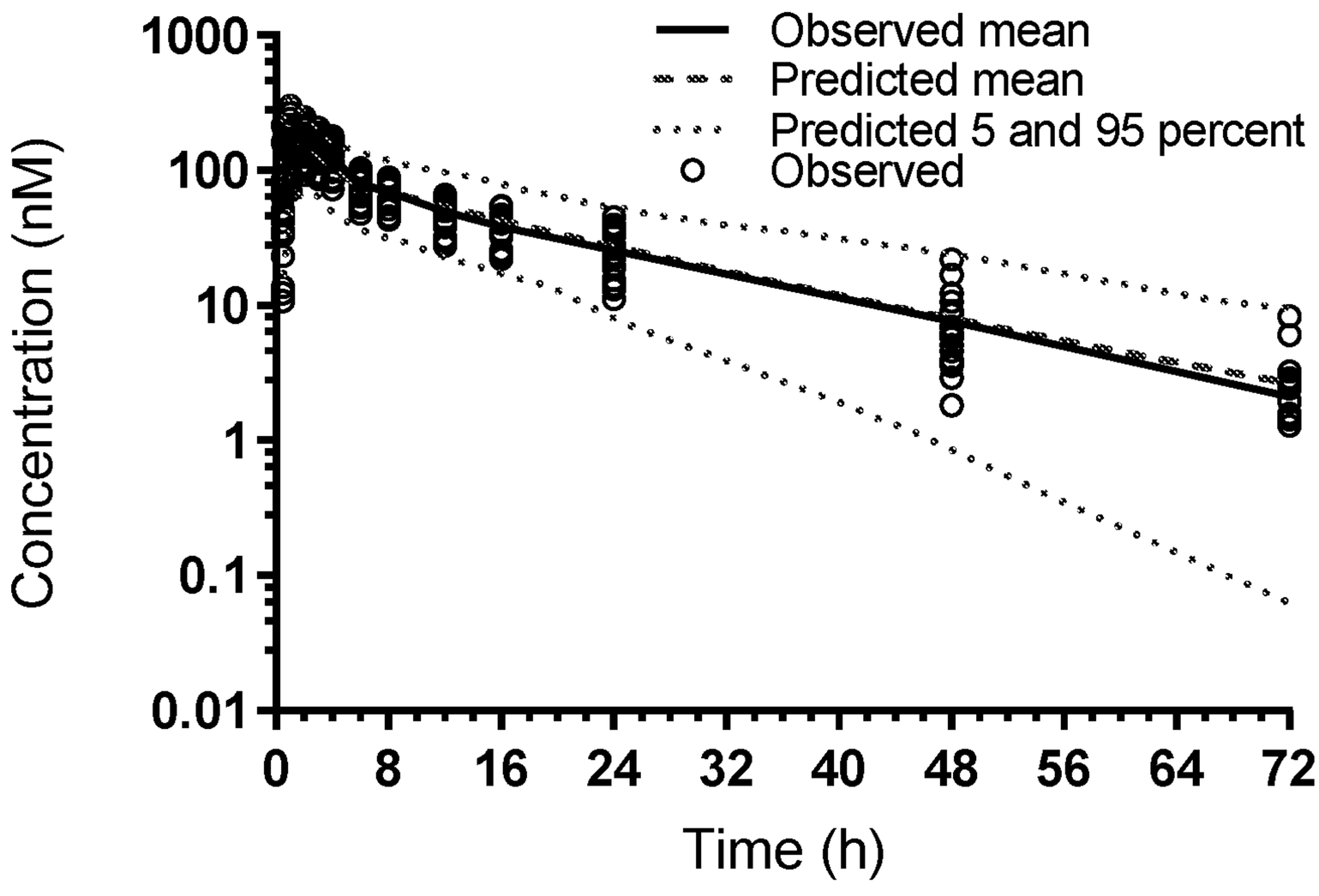

Observed mean
Predicted mean
Predicted 5 and 95 percent
Observed
Concentration (nM)
1000
100
10
1
0.1
0.01
0
8
16
24
32
40
48
56
64
72
Time (h)

FIG. 4A

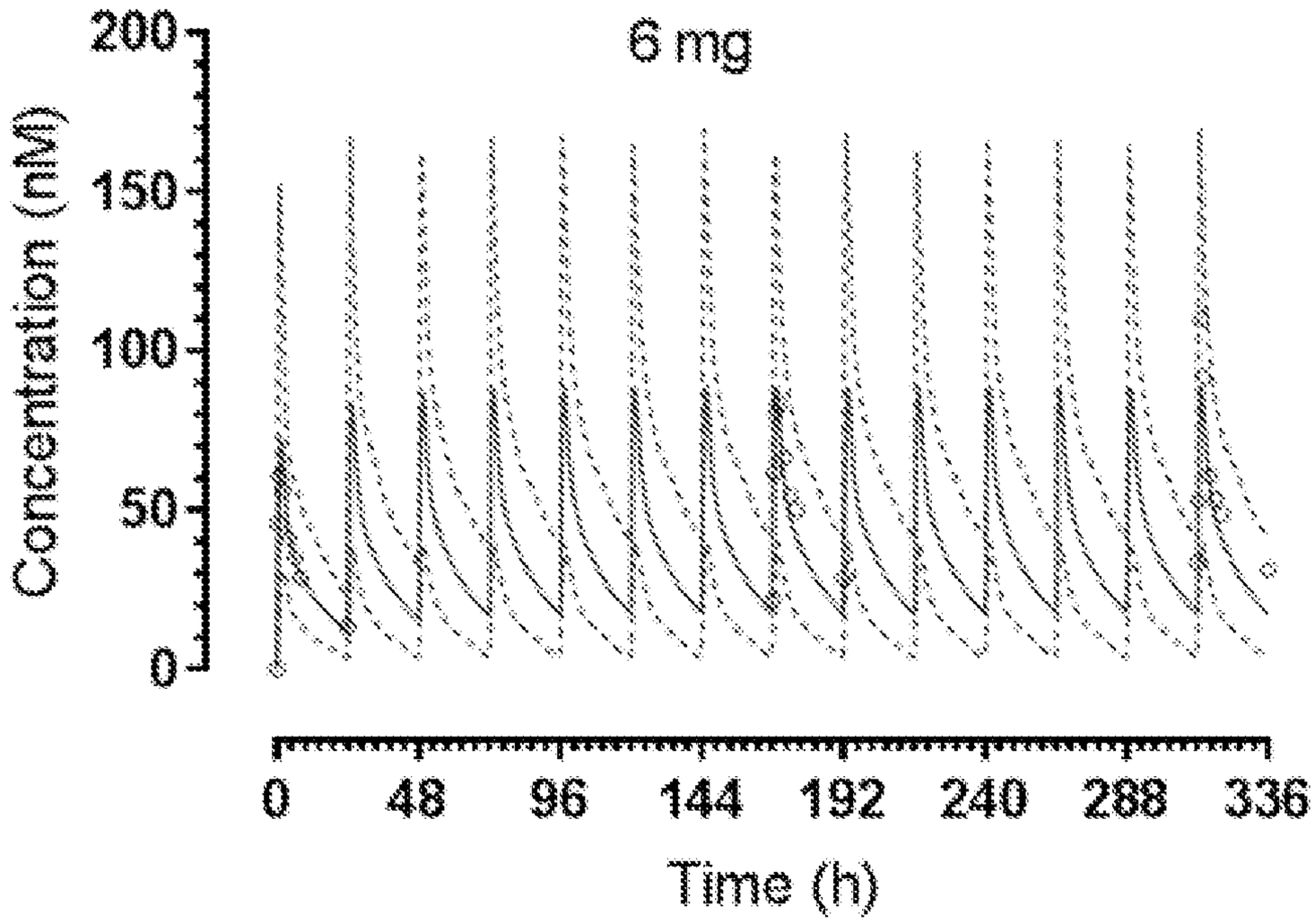

6 mg
Concentration (nM)
200
150
100
50
0
0
48
96
144
192
240
288
336
Time (h)

FIG. 4B

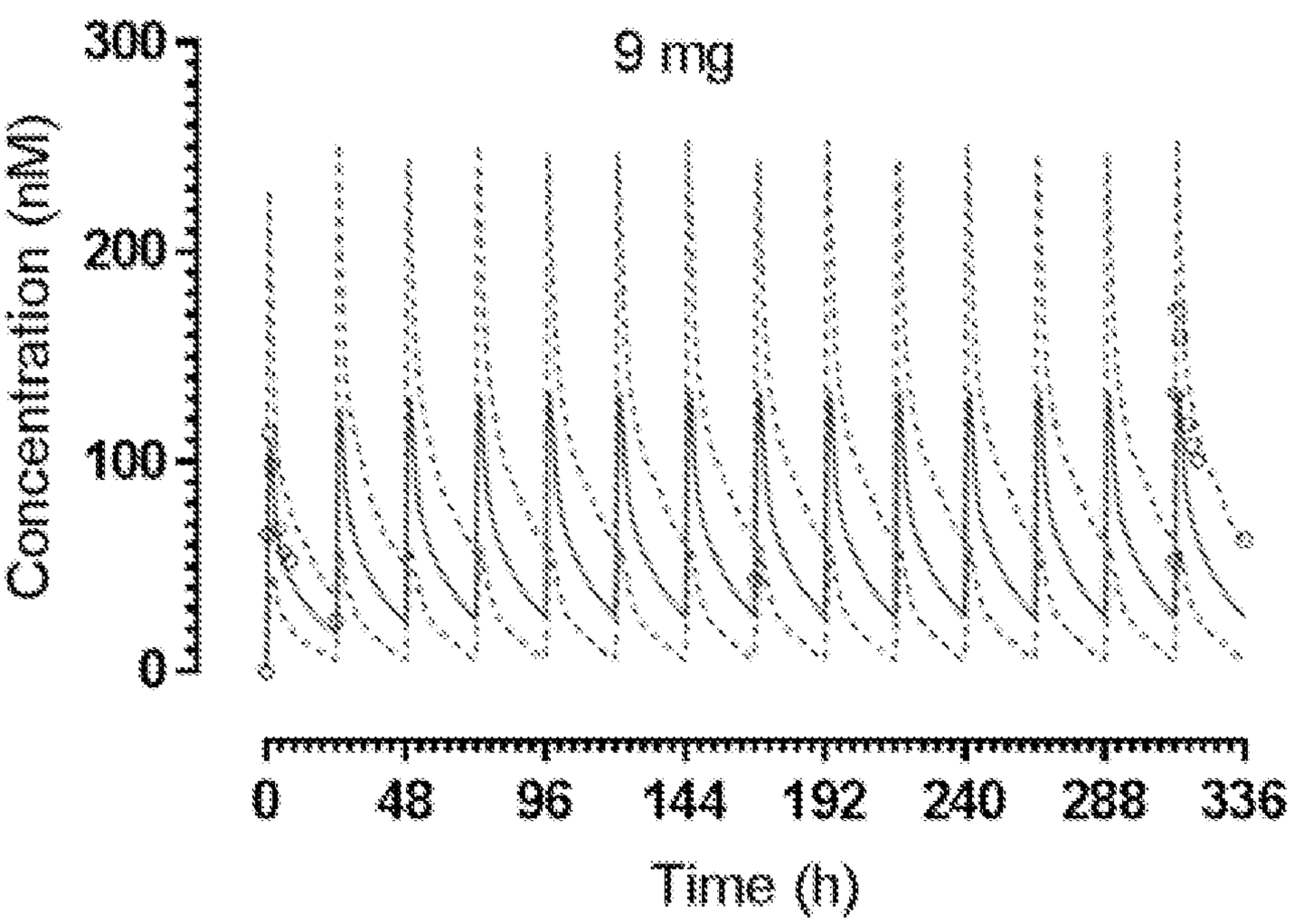

9 mg
Concentration (nM)
300
200
100
0
0
48
96
144
192
240
288
336
Time (h)

FIG. 4C

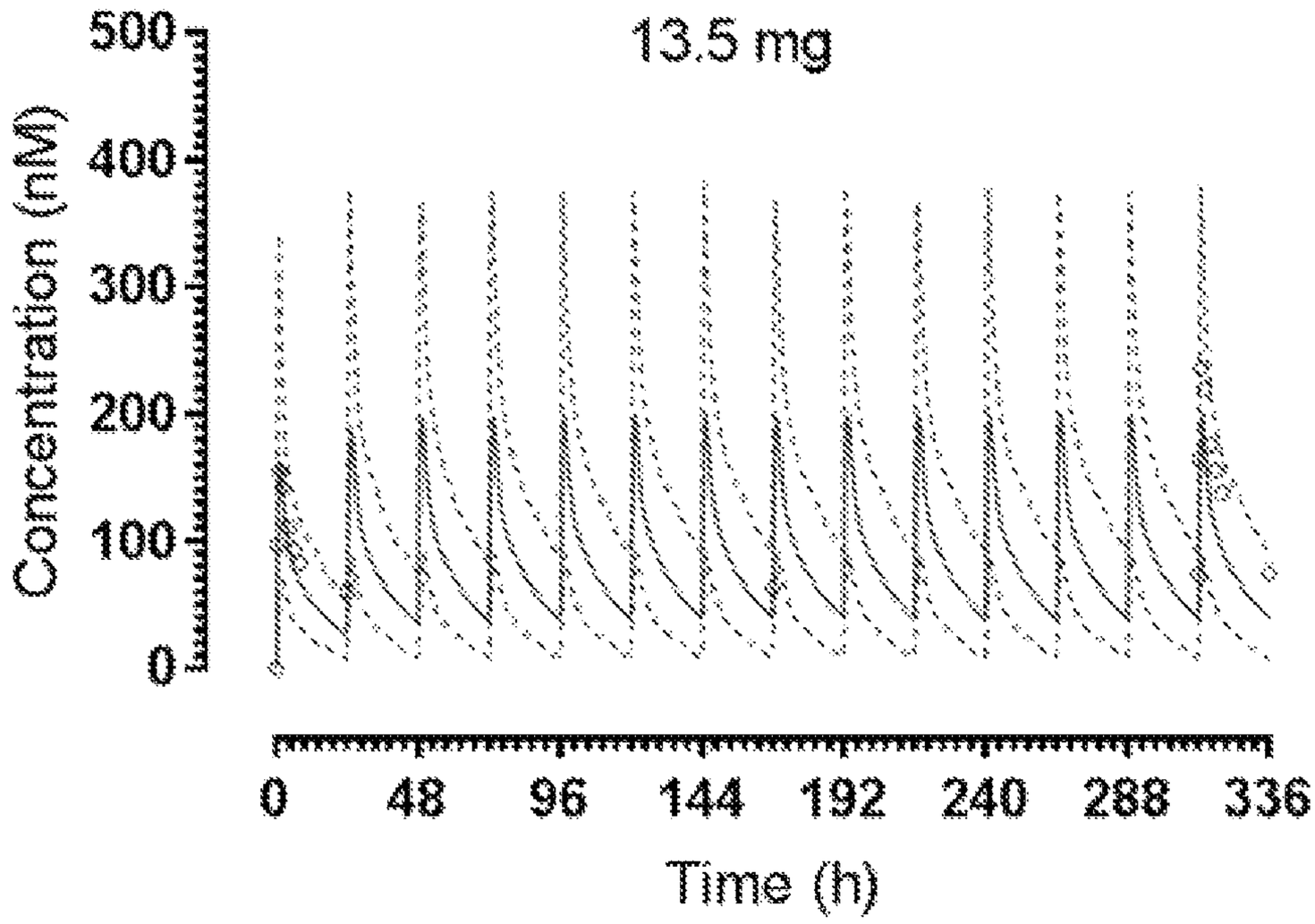

13.5 mg
Concentration (nM)
500
400
300
200
100
0
0
48
96
144
192
240
288
336
Time (h)

FIG. 4D

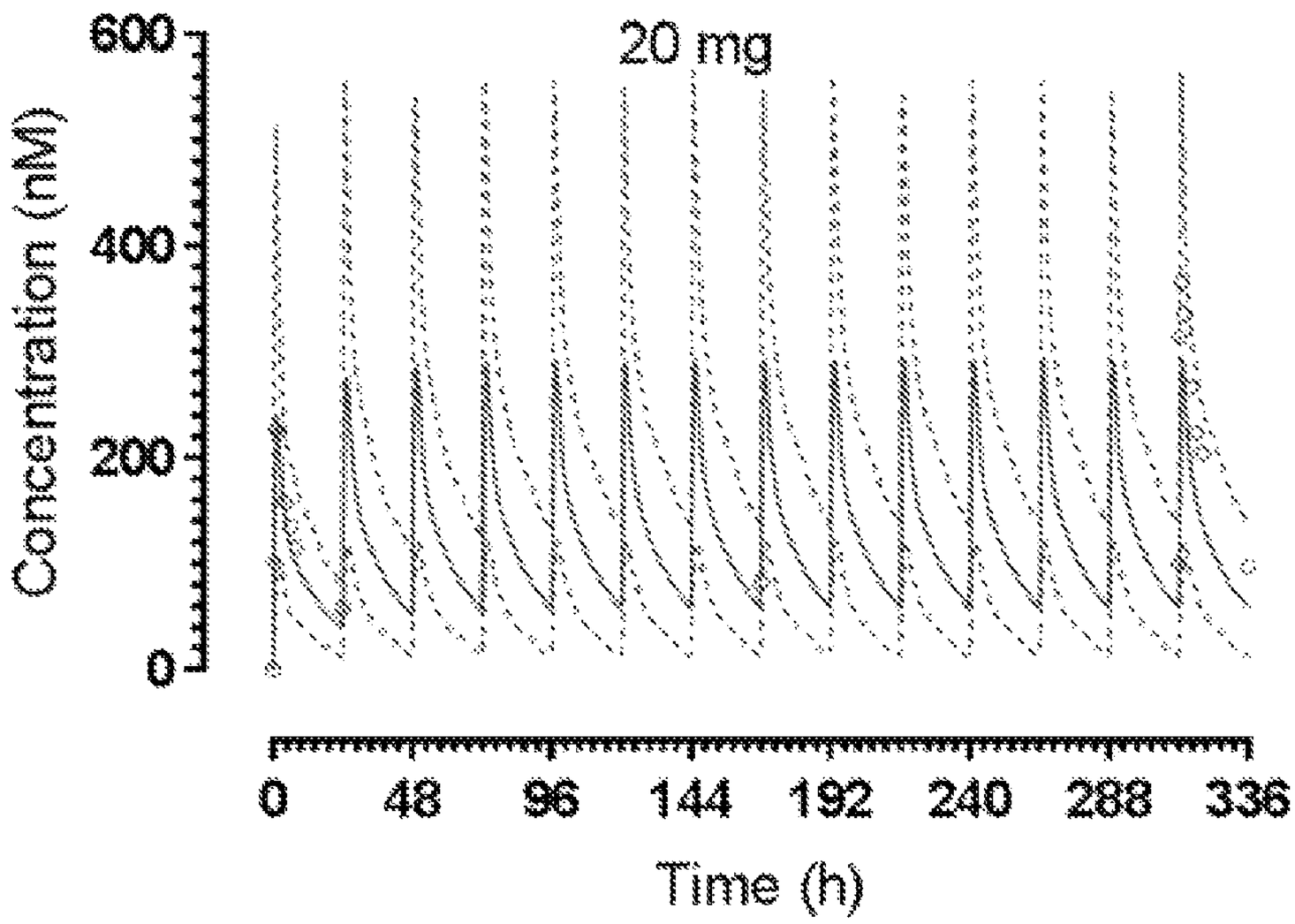

20 mg
Concentration (nM)
600
400
200
0
0
48
96
144
192
240
288
336
Time (h)

FIG. 5A

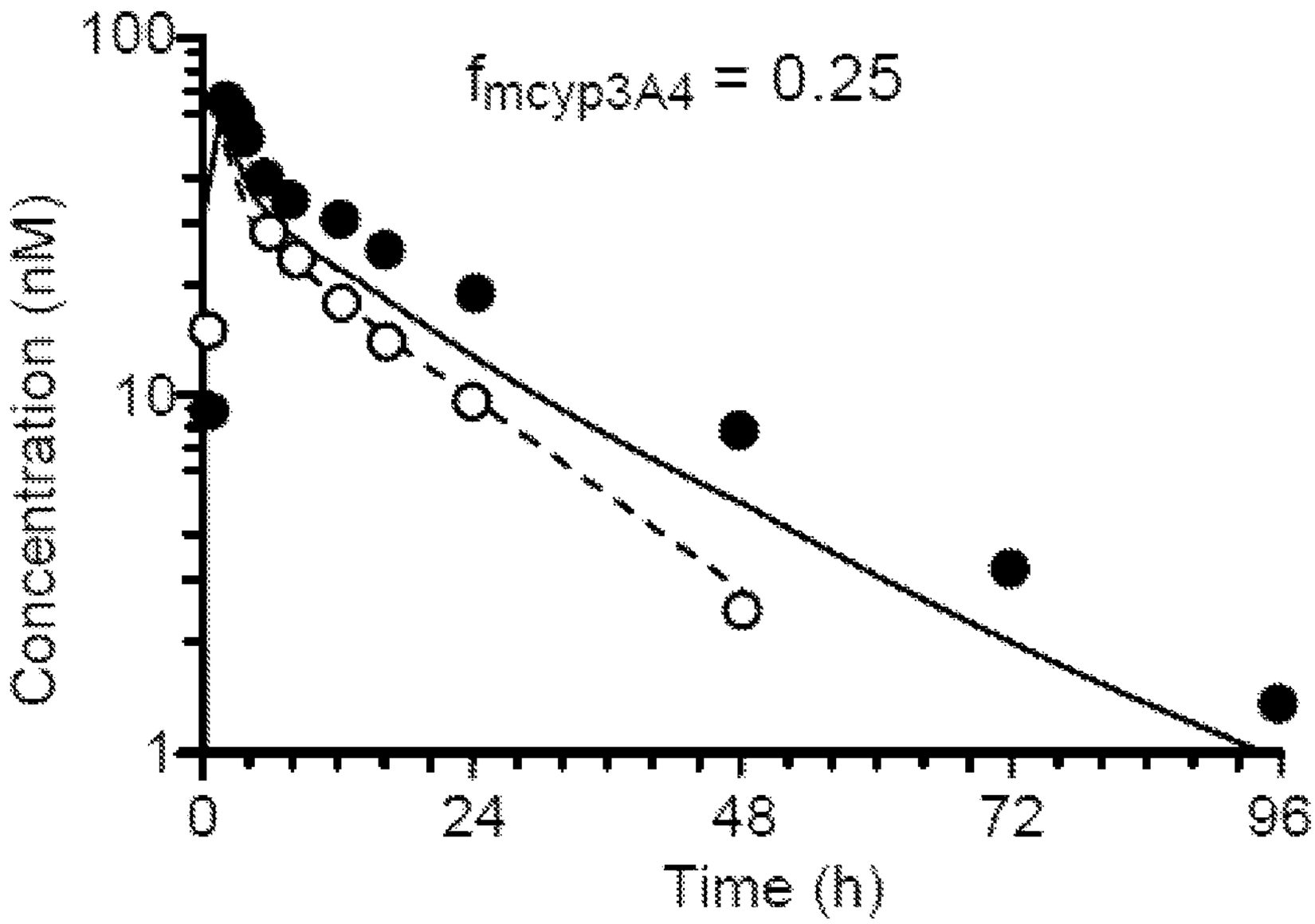

$f_{mcyp3A4}$ = 0.25
100
10
1
Concentration (nM)
0
24
48
72
96
Time (h)

FIG. 5B

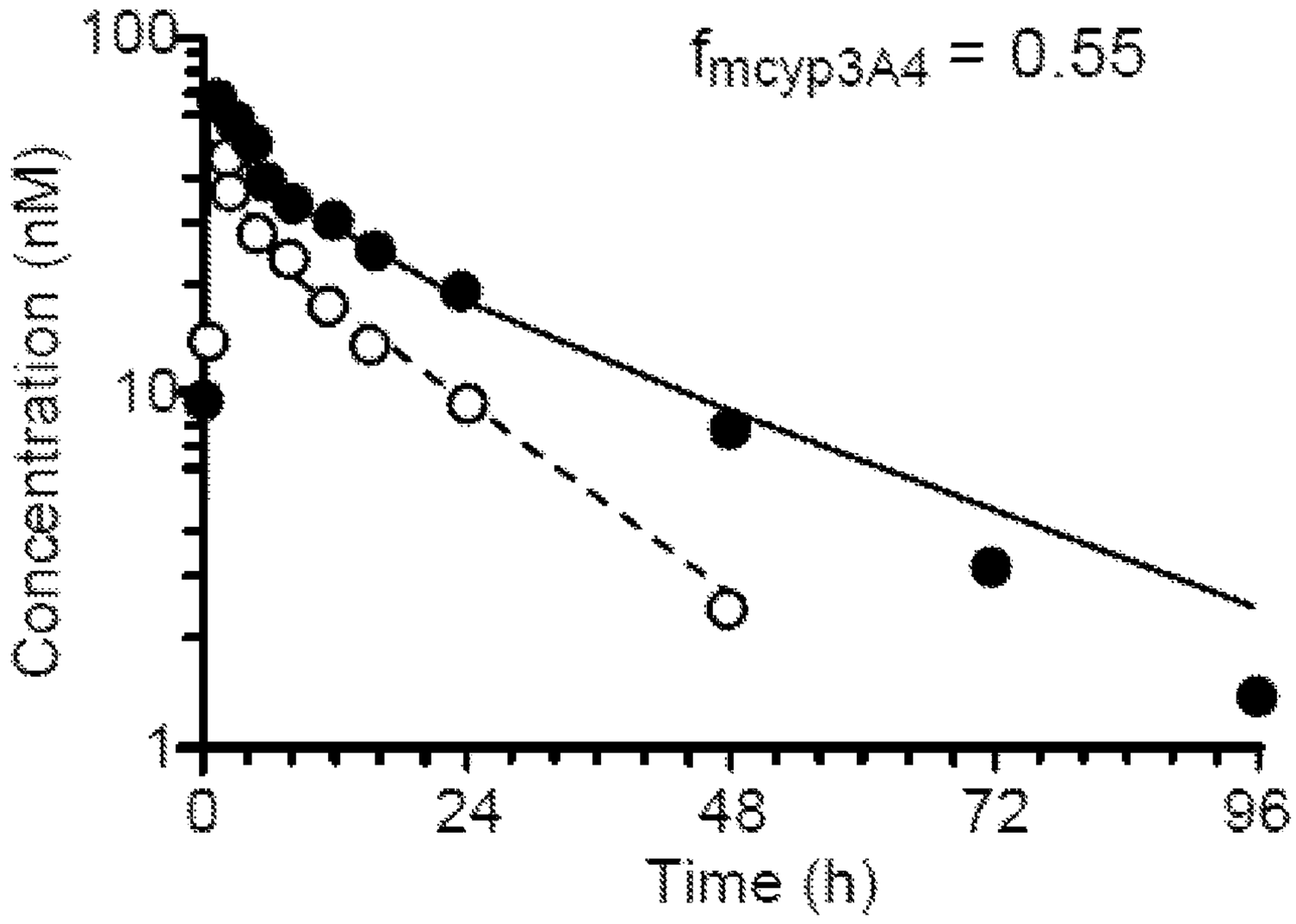

$f_{mcyp3A4}$ = 0.55
100
10
1
Concentration (nM)
0
24
48
72
96
Time (h)

FIG. 5C

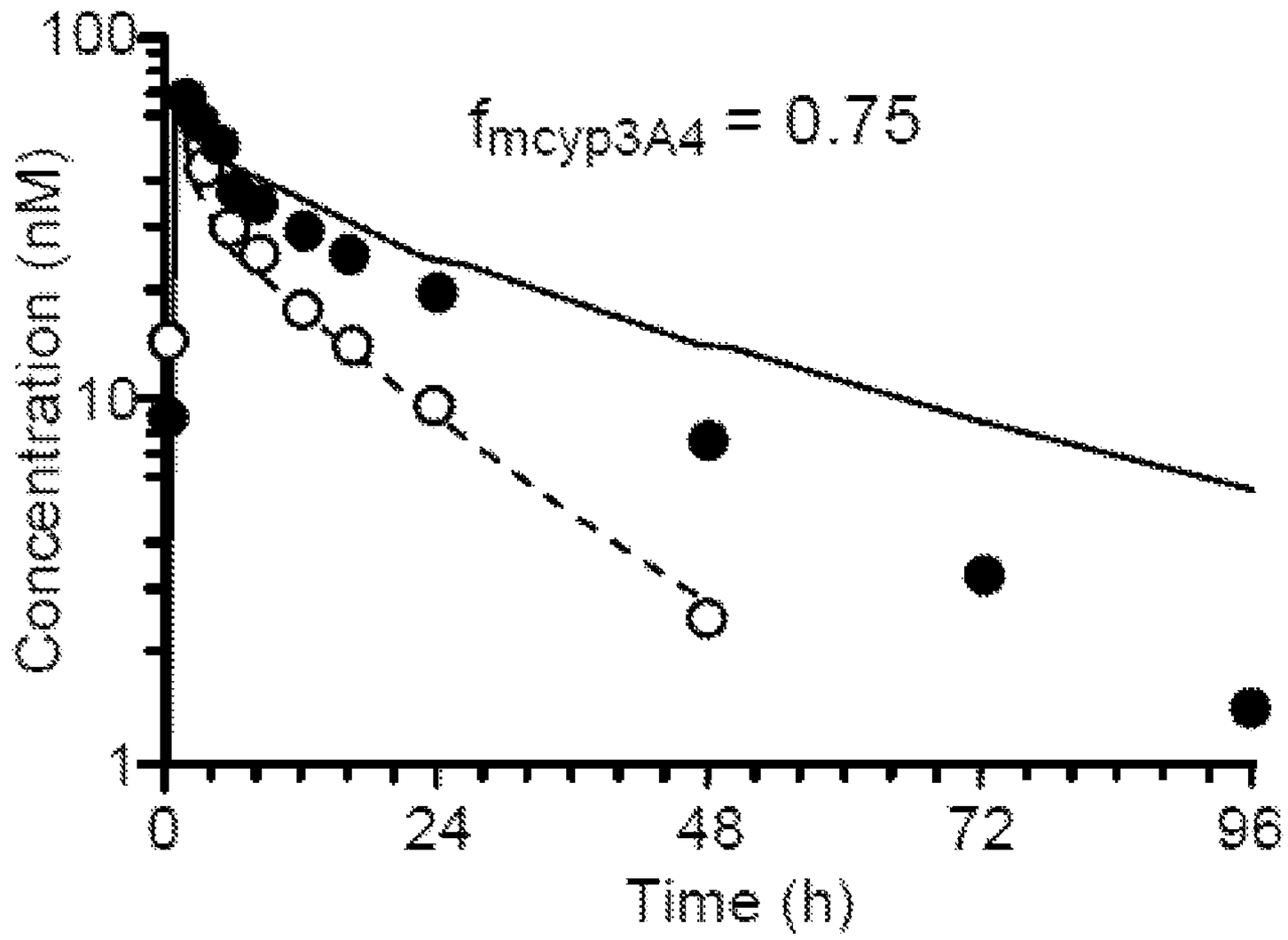

100
10
1
0
24
48
72
96
Concentration (nM)
Time (h)
fmcyp3A4 = 0.75

FIG. 5D

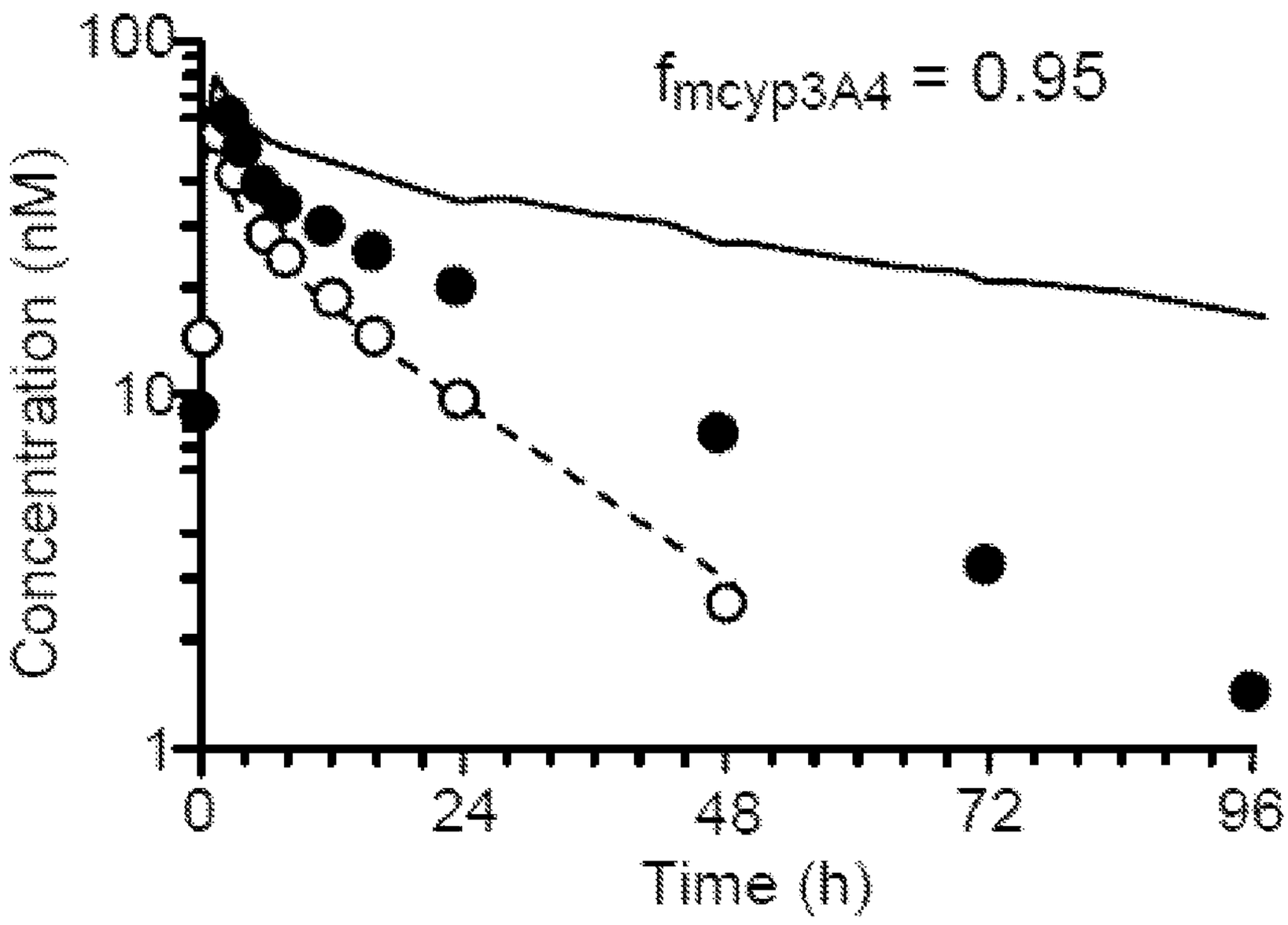

100
10
1
0
24
48
72
96
Concentration (nM)
Time (h)
fmcyp3A4 = 0.95

FIG. 6A

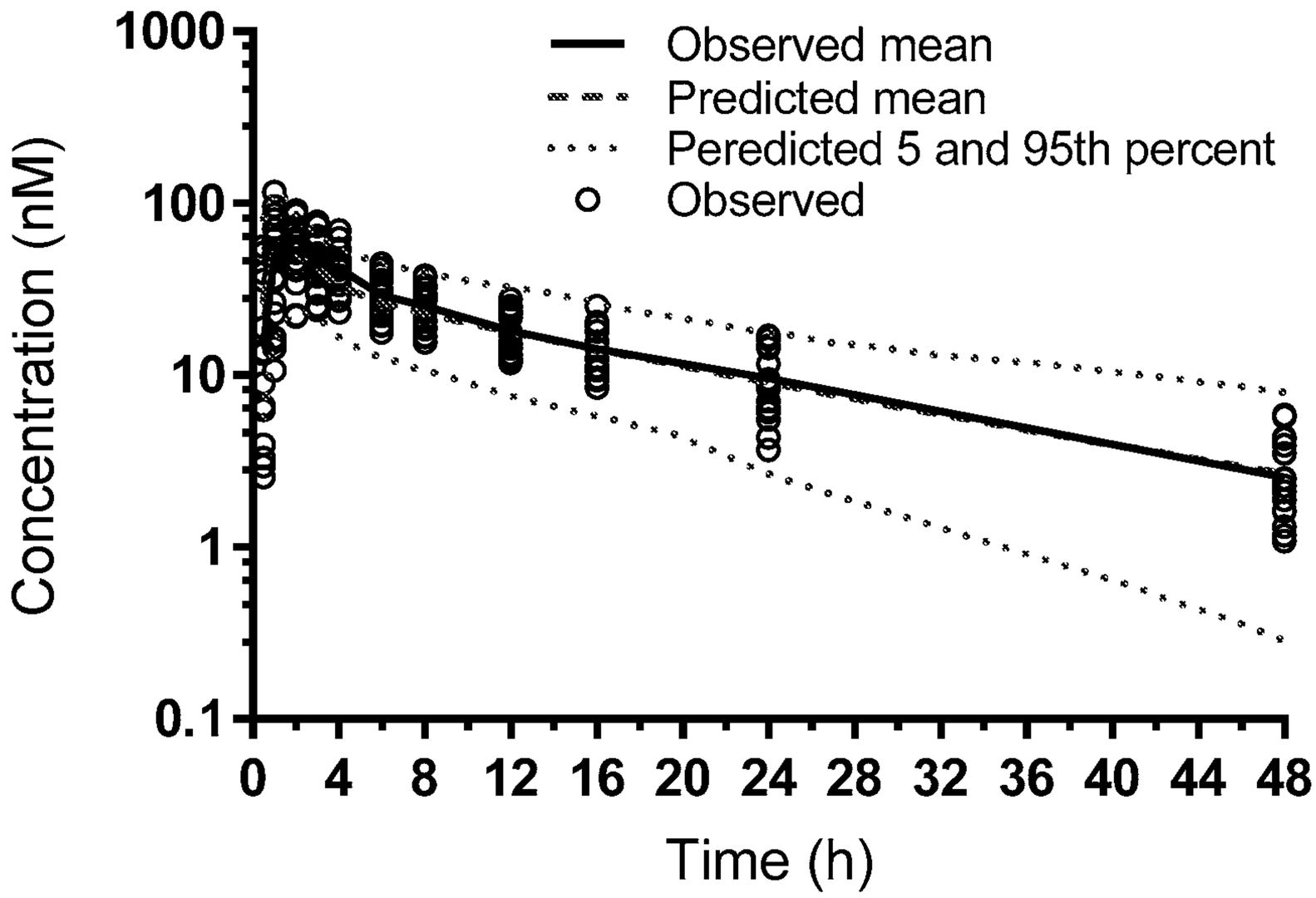

Observed mean
Predicted mean
Peredicted 5 and 95th percent
Observed
Concentration (nM)
1000
100
10
1
0.1
0
4
8
12
16
20
24
28
32
36
40
44
48
Time (h)

FIG. 6B

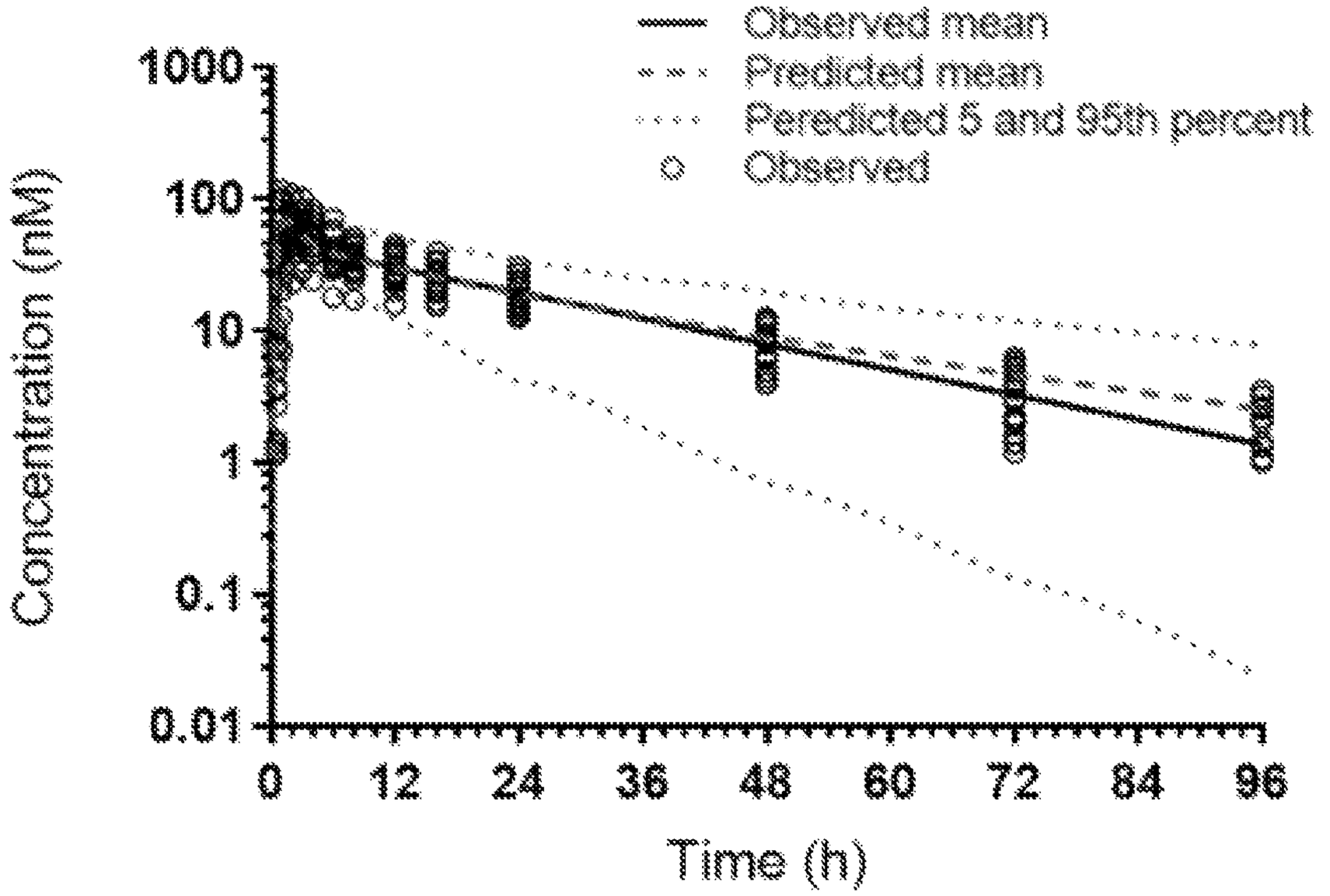

Observed mean
Predicted mean
Peredicted 5 and 95th percent
Observed
Concentration (nM)
1000
100
10
1
0.1
0.01
0
12
24
36
48
60
72
84
96
Time (h)

FIG. 7A

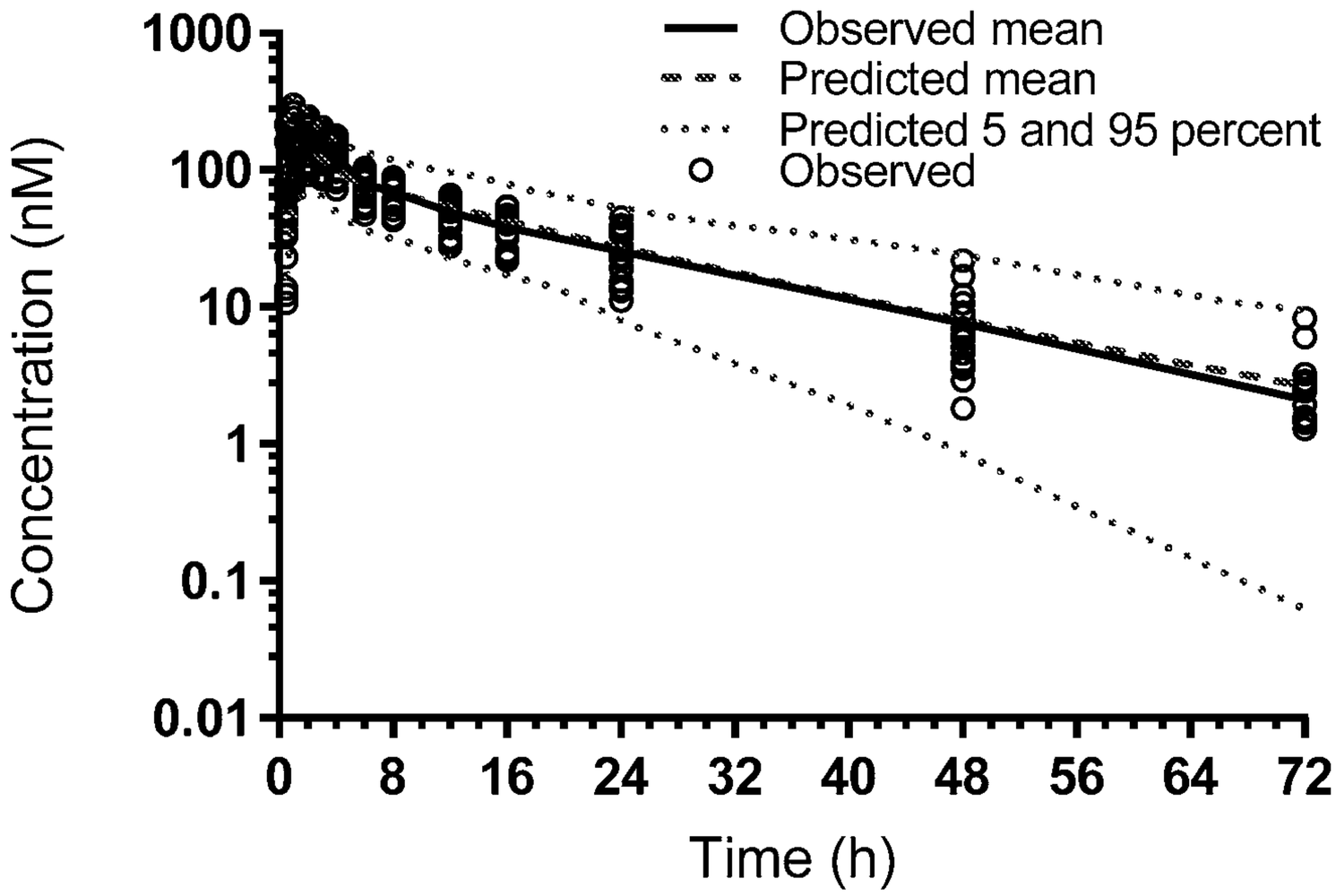

Observed mean
Predicted mean
Predicted 5 and 95 percent
Observed
Concentration (nM)
1000
100
10
1
0.1
0.01
0
8
16
24
32
40
48
56
64
72
Time (h)

FIG. 7B

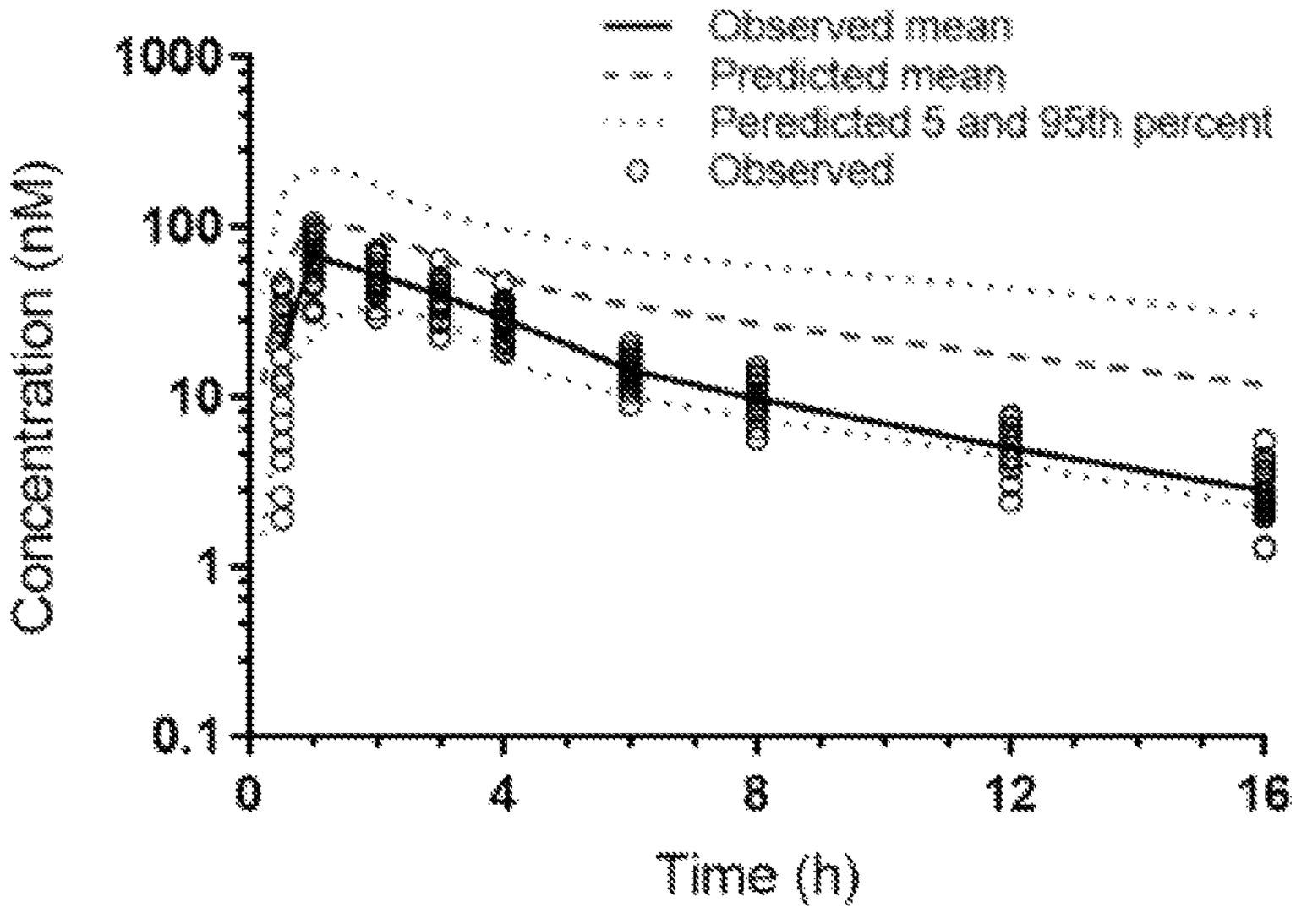
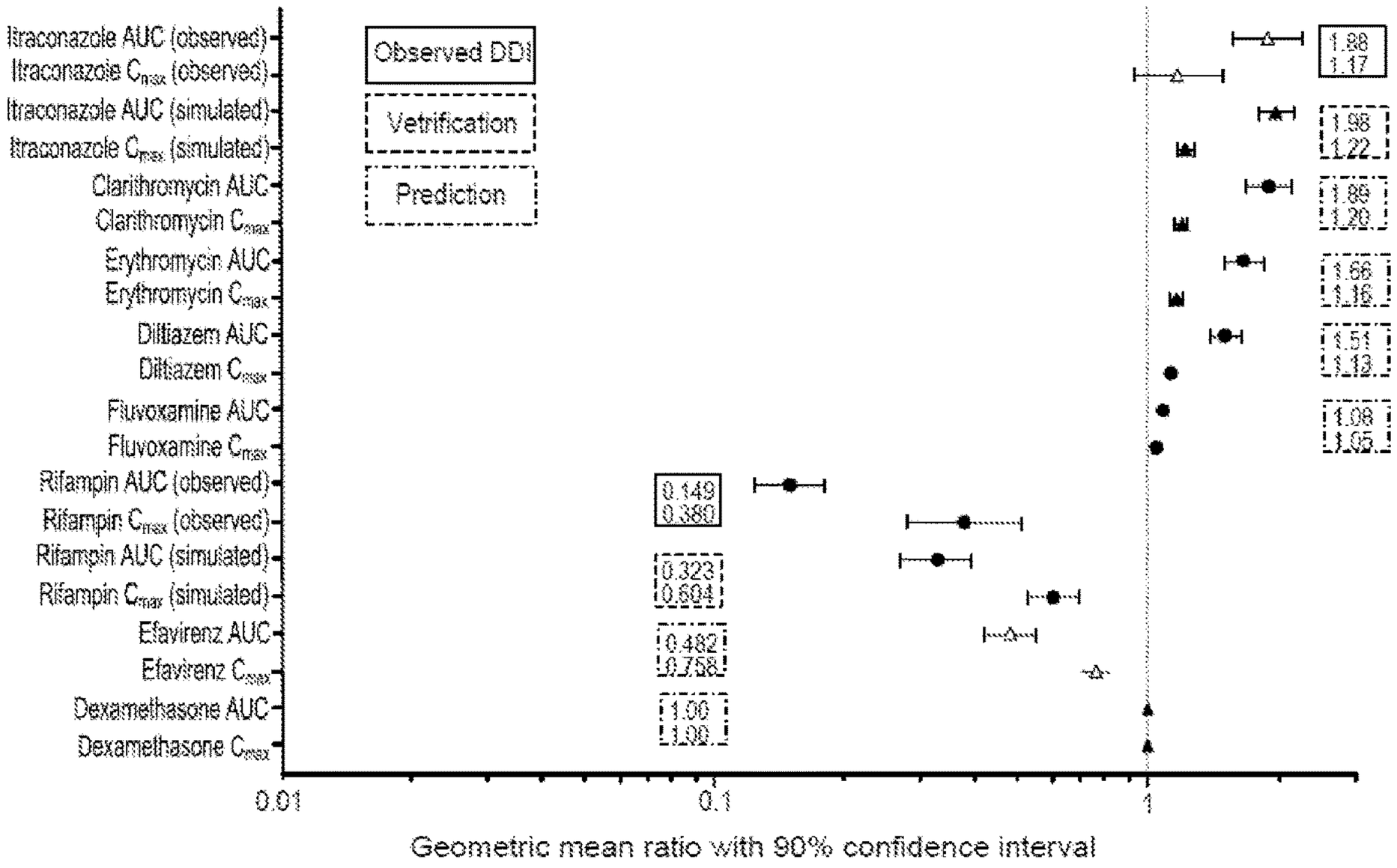

Observed mean
Predicted mean
Peredicted 5 and 95th percent
Observed
Concentration (nM)
1000
100
10
1
0.1
0
4
8
12
16
Time (h)

FIG. 8


Itraconazole AUC (observed)
Itraconazole C_{max} (observed)
Itraconazole AUC (simulated)
Itraconazole C_{max} (simulated)
Clarithromycin AUC
Clarithromycin C_{max}
Erythromycin AUC
Erythromycin C_{max}
Diltiazem AUC
Diltiazem C_{max}
Fluvoxamine AUC
Fluvoxamine C_{max}
Rifampin AUC (observed)
Rifampin C_{max} (observed)
Rifampin AUC (simulated)
Rifampin C_{max} (simulated)
Efavirenz AUC
Efavirenz C_{max}
Dexamethasone AUC
Dexamethasone C_{max}
Observed DDI
Vetrification
Prediction
1.88
1.17
1.98
1.22
1.89
1.20
1.66
1.16
1.51
1.13
1.08
1.05
0.149
0.380
0.323
0.604
0.482
0.758
1.00
1.00
0.01
0.1
1
Geometric mean ratio with 90% confidence interval

METHODS OF TREATING CANCER WITH AN FGFR INHIBITOR

FIELD OF THE INVENTION

This application relates to methods of treating cancer in a patient in need thereof, comprising administering a Fibroblast Growth Factor Receptors (FGFR) inhibitor to the patient.

BACKGROUND OF THE INVENTION

The Fibroblast Growth Factor Receptors (FGFR) are receptor tyrosine kinases that bind to fibroblast growth factor (FGF) ligands. There are four FGFR proteins (FGFR1-4) that are capable of binding ligands and are involved in the regulation of many physiological processes including tissue development, angiogenesis, wound healing, and metabolic regulation. Upon ligand binding, the receptors undergo dimerization and phosphorylation leading to stimulation of the protein kinase activity and recruitment of many intracellular docking proteins. These interactions facilitate the activation of an array of intracellular signaling pathways including Ras-MAPK, AKT-PI3K, and phospholipase C that are important for cellular growth, proliferation and survival (Reviewed in Eswarakumar et al. Cytokine & Growth Factor Reviews, 2005).

Aberrant activation of this pathway either through overexpression of FGF ligands or FGFR or activating mutations in the FGFRs can lead to tumor development, progression, and resistance to conventional cancer therapies. In human cancer, genetic alterations including gene amplification, chromosomal translocations and somatic mutations that lead to ligand-independent receptor activation have been described. Large scale DNA sequencing of thousands of tumor samples has revealed that components of the FGFR pathway are among the most frequently mutated in human cancer. Many of these activating mutations are identical to germline mutations that lead to skeletal dysplasia syndromes. Mechanisms that lead to aberrant ligand-dependent signaling in human disease include overexpression of FGFs and changes in FGFR splicing that lead to receptors with more promiscuous ligand binding abilities (Reviewed in Knights and Cook Pharmacology & Therapeutics, 2010; Turner and Grose, Nature Reviews Cancer, 2010). Therefore, development of inhibitors targeting FGFR may be useful in the clinical treatment of diseases that have elevated FGF or FGFR activity.

The cancer types in which FGF/FGFRs are implicated include, but are not limited to: carcinomas (e.g., bladder, breast, cervical, colorectal, endometrial, gastric, head and neck, kidney, liver, lung, ovarian, prostate); hematopoietic malignancies (e.g., multiple myeloma, chronic lymphocytic lymphoma, adult T cell leukemia, acute myelogenous leukemia, non-Hodgkin lymphoma, myeloproliferative neoplasms, and Waldenstrom's Macroglubulinemia); and other neoplasms (e.g., glioblastoma, melanoma, and rhabdosarcoma). In addition to a role in oncogenic neoplasms, FGFR activation has also been implicated in skeletal and chondrocyte disorders including, but not limited to, achrondroplasia and craniosynostosis syndromes.

The FGFR4-FGF19 signaling axis, specifically, has been implicated in the pathogenesis of a number of cancers including hepatocellular carcinoma (Heinzle et al., Cur. Pharm. Des. 2014, 20:2881). Ectopic expression of FGF19 in transgenic mice was shown to lead to tumor formation in the liver and a neutralizing antibody to FGF19 was found to inhibit tumor growth in mice. In addition, overexpression of FGFR4 has been observed in a multiple tumor types including hepatocellular carcinoma, colorectal, breast, pancreatic, prostate, lung, and thyroid cancers. Furthermore, activating mutations in FGFR4 have been reported in rhabdomyosarcoma (Taylor et al. JCI 2009, 119:3395).

Inhibitors of FGFR are currently being developed for the treatment of cancer. For example, pemigatinib, or 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-(morpholin-4-ylmethyl)-1,3,4,7-tetrahydro-2H-pyrrolo[3',2': 5,6]pyrido[4,3-d]pyrimidin-2-one, and other small molecule inhibitors of FGFR are reported in e.g., U.S. Pat. No. 9,611,267, and US Publication Nos.: 2012/0165305; 2014/0045814; 2013/0338134; 2014/0171405; 2014/0315902; 2016/0115164; 2016/0244448; 2016/0244449; and 2016/0244450; and U.S. Provisional Application Nos. 62/667,166 and 62/667,040 (corresponding to US Publication Nos.: 2019/0337948 and 2020/0002338, respectively).

It has been estimated that 6.5-23% of adverse reactions from exposure to multiple drugs results from drug-drug interactions. Each year, a number of deaths occur as a result of patients adding concomitant prescription pharmaceutical products to their existing medication regimen. Thus, there needs for increased understanding of drug-drug interactions and improved methods for administering cancer therapeutics (e.g., pemigatinib) to individuals who are concomitantly being treated with other active agents.

SUMMARY OF THE INVENTION

Provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of a CYP3A4 perpetrator.

Also provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises:

(a) determining if the patient is receiving administration of a CYP3A4 perpetrator; and

(b) administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of the CYP3A4 perpetrator.

Also provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises:

(a) discontinuing administration of a CYP3A4 perpetrator to the patient for a time period of about 5 or more half-lives of the CYP3A4 perpetrator; and

(b) administering a therapeutically effective amount of pemigatinib to the patient.

In some embodiments, the CYP3A4 perpetrator is a strong CYP3A4 inhibitor. In some embodiments, the CYP3A4 perpetrator is a moderate to strong CYP3A4 inducer.

Provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises:

(a) determining if the patient is receiving administration of a strong CYP3A4 inhibitor; and

(b) administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of a strong CYP3A4 inhibitor.

Provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises:

(a) determining if the patient is receiving administration of a moderate to strong CYP3A4 inducer; and

(b) administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of a moderate to strong CYP3A4 inducer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the plasma concentration of pemigatinib in healthy volunteers after administration of pemigatinib with or without coadministration of itraconazole.

FIG. **2** shows the plasma concentration of pemigatinib in healthy volunteers after administration of pemigatinib with or without coadministration of rifampin.

FIG. **3**A shows the observed and simulated mean plasma concentration-time profiles for pemigatinib following a single oral dose of 4.5 mg pemigatinib tablet alone.

FIG. **3**B shows the observed and simulated mean plasma concentration-time profiles for pemigatinib following a single oral dose of 13.5 mg pemigatinib tablet alone.

FIG. **4**A shows the simulated and observed mean plasma concentration-time profiles of pemigatinib following a multiple oral dose of pemigatinib tablets at 6 mg in cancer patients. The solid line shows the simulated mean. The dashed line shows the simulated 5% and 95%. The circles show the observed data.

FIG. **4**B shows the simulated and observed mean plasma concentration-time profiles of pemigatinib following a multiple oral dose of pemigatinib tablets at 9 mg in cancer patients. The solid line shows the simulated mean. The dashed line shows the simulated 5% and 95%. The circles show the observed data.

FIG. **4**C shows the simulated and observed mean plasma concentration-time profiles of pemigatinib following a multiple oral dose of pemigatinib tablets at 13.5 mg in cancer patients. The solid line shows the simulated mean. The dashed line shows the simulated 5% and 95%. The circles show the observed data.

FIG. **4**D shows the simulated and observed mean plasma concentration-time profiles of pemigatinib following a multiple oral dose of pemigatinib tablets at 20 mg in cancer patients. The solid line shows the simulated mean. The dashed line shows the simulated 5% and 95%. The circles show the observed data.

FIG. **5**A shows the Sensitivity analysis of pemigatinib $f_{mCYP3\ A4}$ on drug interaction with itraconazole, at $f_{mCYP3\ A4}$=0.25. The dashed line shows the simulated mean for pemigatinib alone; the solid line shows the simulated mean for pemigatinib when co-administered with itraconazole; the open circle shows the observed mean for pemigatinib alone; the closed circle shows the observed mean for pemigatinib when co-administered with itraconazole.

FIG. **5**B shows the Sensitivity analysis of pemigatinib $f_{mCYP3\ A4}$ on drug interaction with itraconazole, at $f_{mCYP3\ A4}$=0.55. The dashed line shows the simulated mean for pemigatinib alone; the solid line shows the simulated mean for pemigatinib when co-administered with itraconazole; the open circle shows the observed mean for pemigatinib alone; the closed circle shows the observed mean for pemigatinib when co-administered with itraconazole.

FIG. **5**C shows the Sensitivity analysis of pemigatinib $f_{mCYP3\ A4}$ on drug interaction with itraconazole, at $f_{mCYP3\ A4}$=0.75. The dashed line shows the simulated mean for pemigatinib alone; the solid line shows the simulated mean for pemigatinib when co-administered with itraconazole; the open circle shows the observed mean for pemigatinib alone; the closed circle shows the observed mean for pemigatinib when co-administered with itraconazole.

FIG. **5**D shows the Sensitivity analysis of pemigatinib $f_{mCYP3\ A4}$ on drug interaction with itraconazole, at $f_{mCYP3\ A4}$=0.95. The dashed line shows the simulated mean for pemigatinib alone; the solid line shows the simulated mean for pemigatinib when co-administered with itraconazole; the open circle shows the observed mean for pemigatinib alone; the closed circle shows the observed mean for pemigatinib when co-administered with itraconazole.

FIG. **6**A shows the simulated and observed plasma concentration-time profiles of pemigatinib following a single oral dose of 4.5 mg pemigatinib tablets alone (without itraconazole administration).

FIG. **6**B shows the simulated and observed plasma concentration-time profiles of pemigatinib following a single oral dose of 4.5 mg pemigatinib tablets coadministered with itraconazole.

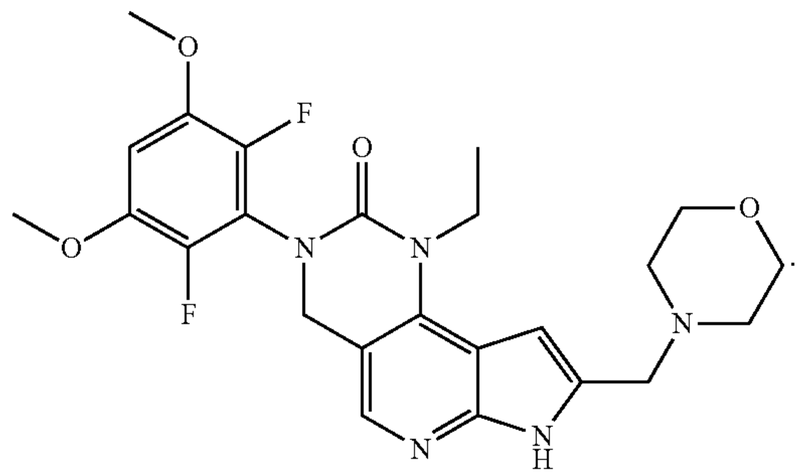
FIG. **7**A shows the simulated and observed plasma concentration-time profiles of pemigatinib following a single oral dose of 13.5 mg pemigatinib tablets alone (without rifampin administration).

FIG. **7**B shows the simulated and observed plasma concentration-time profiles of pemigatinib following a single oral dose of 13.5 mg pemigatinib tablets coadministered with rifampin.

FIG. **8** shows the observed and simulated pemigatinib AUC and C_{max} ratios with various CYP3A4 inhibitors and inducers.

DETAILED DESCRIPTION

The present disclosure is directed to, inter alia, methods of treating cancer in a patient in need thereof, comprising administering pemigatinib, which is 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-(morpholin-4-ylmethyl)-1,3,4,7-tetrahydro-2H-pyrrolo[3',2': 5,6]pyrido[4,3-d]pyrimidin-2-one, having the structure shown below:



Pemigatinib

Pemigatinib is described in U.S. Pat. No. 9,611,267, the entirety of which is incorporated herein by reference. Pemigatinib is further described in US Publication Nos.: 2019/0337948 and 2020/0002338, the entireties of which are incorporated herein by reference.

Provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of a CYP3A4 perpetrator.

Also provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises:

(a) determining if the patient is receiving administration of a CYP3A4 perpetrator; and

(b) administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of the CYP3A4 perpetrator.

Also provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises:

(a) discontinuing administration of a CYP3A4 perpetrator to the patient for a time period of about 5 or more half-lives of the CYP3A4 perpetrator; and

(b) administering a therapeutically effective amount of pemigatinib to the patient.

Also provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises:

(a) discontinuing administration of a CYP3A4 perpetrator to the patient for a time period, wherein the time period is the shorter of i) about 5 or more half-lives of the CYP3A4 perpetrator and ii) 14 days; and

(b) administering a therapeutically effective amount of pemigatinib to the patient.

In some embodiments, the CYP3A4 perpetrator is a strong CYP3A4 inhibitor. In some embodiments, the CYP3A4 perpetrator is a moderate to strong CYP3A4 inducer.

In some embodiments, provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of a strong CYP3A4 inhibitor.

In some embodiments, provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of itraconazole.

In some embodiments, provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises:

(a) determining if the patient is receiving administration of a strong CYP3A4 inhibitor; and

(b) administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of a strong CYP3A4 inhibitor.

Also provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises:

(a) discontinuing administration of a strong CYP3A4 inhibitor to the patient for a time period of about 5 or more half-lives of the strong CYP3A4 inhibitor; and

(b) administering a therapeutically effective amount of pemigatinib to the patient.

In some embodiments, the time period of discontinuing administration of a strong CYP3A4 inhibitor to the patient is 6 or more half-lives of the strong CYP3A4 inhibitor.

In some embodiments, the time period of discontinuing administration of a strong CYP3A4 inhibitor to the patient is 7 or more half-lives of the strong CYP3A4 inhibitor.

Also provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises:

(a) discontinuing administration of a strong CYP3A4 inhibitor to the patient for a time period of about 5 or more half-lives of the strong CYP3A4 inhibitor; and

(b) administering a therapeutically effective amount of pemigatinib to the patient while avoiding the administration of the strong CYP3A4 inhibitor during treatment.

Also provided herein is a method of treating cancer in a patient in need thereof, comprising orally administering an adjusted daily dosage amount of pemigatinib to the patient who is receiving concomitant administration of a strong CYP3A4 inhibitor, wherein the adjusted daily dosage amount of pemigatinib is about 25% to about 75% of an intended daily dosage amount of pemigatinib, and wherein:

(a) the intended daily dosage amount of pemigatinib is a dosage amount suitable for the patient if the patient is not receiving a concomitant strong CYP3A4 inhibitor; or

(b) the intended daily dosage amount of pemigatinib is about 9 mg to 13.5 mg for an adult patient.

In some embodiments, the administration of pemigatinib comprises:

(a) a continuous daily administration of an intended amount or adjusted amount of pemigatinib to the patient in need thereof; or

(b) a 21-day dosing cycle comprising: 14 days of daily administration of an intended amount or adjusted amount of pemigatinib to the patient in need thereof and 7 days without administration of pemigatinib.

In some embodiments, the adjusted daily dosage amount of pemigatinib is about 40% to about 70% of the intended dosage amount of pemigatinib. In some embodiments, the adjusted daily dosage amount of pemigatinib is about 50% of the intended dosage amount of pemigatinib. In some embodiments, the adjusted daily dosage amount of pemigatinib is about 60% to about 70% of the intended dosage amount of pemigatinib. In some embodiments, the adjusted daily dosage amount of pemigatinib is about 25%, about 30%, about 40%, about 50%, about 60%, about 70%, or about 75% of the intended dosage amount of pemigatinib.

In some embodiments, the intended daily dosage amount of pemigatinib is the dosage amount suitable for the patient if the patient is not receiving administration of a strong CYP3A4 inhibitor. In some embodiments, the intended daily dosage of pemigatinib is about 9 mg to about 13.5 mg. In some embodiments, the adjusted daily dosage amount of pemigatinib is about 9 mg for patients on an intended dose of about 13.5 mg of pemigatinib. In some embodiments, the adjusted daily dosage amount of pemigatinib is about 4.5 mg for patients on an intended dose of about 9 mg of pemigatinib. In some embodiments, the adjusted daily dosage amount of pemigatinib is about 4.5 mg to about 9 mg.

In some embodiments, the concomitant administration of pemigatinib and a strong CYP3A4 inhibitor provides an altered therapeutic effect or adverse reaction profile of pemigatinib.

Also provided herein is a method of treating cancer in a patient in need thereof, wherein the method comprises orally administering a therapeutically effective amount of pemigatinib to the patient and any one or more of the following:

(a) advising the patient that strong CYP3A4 inhibitors should be avoided or discontinued;

(b) advising the patient that use of pemigatinib in patients being treated with strong CYP3A4 inhibitors is contraindicated;

(c) advising the patient that the concomitant administration of pemigatinib and strong CYP3A4 inhibitors can alter the therapeutic effect of pemigatinib;

(d) advising the patient that strong CYP3A4 inhibitors should be used with caution in patients receiving pemigatinib due to the potential for reduced pemigatinib clearance;

(e) advising the patient that the concomitant administration of pemigatinib and strong CYP3A4 inhibitors resulted in about 2-fold decrease in pemigatinib clearance; or

(f) advising the patient that the concomitant administration of pemigatinib and strong CYP3A4 inhibitors resulted in about 2-fold increase in exposure to pemigatinib.

In some embodiments, the method comprises advising the patient that strong CYP3A4 inhibitors should be avoided or discontinued. In some embodiments, the method comprises advising the patient that use of pemigatinib in patients being treated with strong CYP3A4 inhibitors is contraindicated. In some embodiments, the method comprises advising the patient that the concomitant administration of pemigatinib and strong CYP3A4 inhibitors can alter the therapeutic effect of pemigatinib. In some embodiments, the method comprises advising the patient that the concomitant administration of pemigatinib and strong CYP3A4 inhibitors resulted in about 2-fold increase in exposure to pemigatinib. In some embodiments, the method comprises advising the patient that strong CYP3A4 inhibitors should be used with caution in patients receiving pemigatinib due to the potential for reduced pemigatinib clearance. In some embodiments, the method comprises advising the patient that the concomitant administration of pemigatinib and strong CYP3A4 inhibitors resulted in about 2-fold decrease in pemigatinib clearance.

In some embodiments, the adjusted daily dosage amount of pemigatinib is the amount that provides $t_{1/2}$ values substantially the same as $t_{1/2}$ values when pemigatinib is administered alone. In some embodiments, the targeted $t_{1/2}$ value for a patient who is also receiving concomitant administration of pemigatinib and a strong CYP3A4 inhibitor is substantially the same as the $t_{1/2}$ value if the patient is receiving administration of pemigatinib alone. In some embodiments, the $t_{1/2}$ when 4.5 mg of pemigatinib is administered alone is about 12 hours. In some embodiments, the $t_{1/2}$ when 4.5 mg of pemigatinib is administered alone is about 11 hours to about 13 hours. In some embodiments, the $t_{1/2}$ when 4.5 mg of pemigatinib is administered alone is about 10 hours to about 14 hours. In some embodiments, the $t_{1/2}$ when 13.5 mg of pemigatinib is administered alone is about 13 hours. In some embodiments, the $t_{1/2}$ when 13.5 mg of pemigatinib is administered alone is about 12 hour to about 14 hours. In some embodiments, the $t_{1/2}$ when 13.5 mg of pemigatinib is administered alone is about 11 hours to about 15 hours. In some embodiments, the $t_{1/2}$ when 13.5 mg of pemigatinib is administered alone is about 10 hours to about 16 hours.

In some embodiments, the adjusted daily dosage amount of pemigatinib is the amount that provides C_{max} values substantially the same as C_{max} values when pemigatinib is administered alone. In some embodiments, the targeted C_{max} value for a patient who is also receiving concomitant administration of pemigatinib and a strong CYP3A4 inhibitor is substantially the same as the C_{max} value if the patient is receiving administration of pemigatinib alone. In some embodiments, the C_{max} when 4.5 mg of pemigatinib is administered alone is about 40 nM to about 80 nM. In some embodiments, the C_{max} when 4.5 mg of pemigatinib is administered alone is about 50 nM to about 70 nM. In some embodiments, the C_{max} when 4.5 mg of pemigatinib is administered alone is about 55 nM to about 65 nM. In some embodiments, the C_{max} when 4.5 mg of pemigatinib is administered alone is about 60 nM. In some embodiments, the C_{max} when 4.5 mg of pemigatinib is administered alone is from about 20 to about 120 nM.

In some embodiments, the C_{max} when 9 mg of pemigatinib is administered alone is from about 50 to about 450 nM.

In some embodiments, the C_{max} when 13.5 mg of pemigatinib is administered alone is about 190 nM to about 210 nM. In some embodiments, the C_{max} when 13.5 mg of pemigatinib is administered alone is about 195 nM to about 205 nM. In some embodiments, the C_{max} when 13.5 mg of pemigatinib is administered alone is about 200 nM. In some embodiments, the C_{max} when 13.5 mg of pemigatinib is administered alone is about 90 nM to about 300 nM. In some embodiments, the C_{max} when 13.5 mg of pemigatinib is administered alone is about 70 nM to about 700 nM.

In some embodiments, the adjusted daily dosage amount of pemigatinib is the amount that provides $AUC_{0-\infty}$ values substantially the same as $AUC_{0-\infty}$ values when pemigatinib is administered alone. In some embodiments, the targeted $AUC_{0-\infty}$ value for a patient who is also receiving concomitant administration of pemigatinib and a strong CYP3A4 inhibitor is substantially the same as the $AUC_{0-\infty}$ value if the patient is receiving administration of pemigatinib alone. In some embodiments, the $AUC_{0-\infty}$ when 4.5 mg of pemigatinib is administered alone is about 500 nM·h to about 900 nM·h. In some embodiments, the $AUC_{0-\infty}$ when 4.5 mg of pemigatinib is administered alone is about 600 nM·h to about 800 nM·h. In some embodiments, the $AUC_{0-\infty}$ when 4.5 mg of pemigatinib is administered alone is about 650 nM·h to about 750 nM·h. In some embodiments, the $AUC_{0-\infty}$ when 4.5 mg of pemigatinib is administered alone is about 700 nM·h. In some embodiments, the $AUC_{0-\infty}$ when 4.5 mg of pemigatinib is administered alone is about 430 nM·h to about 1180 nM·h. In some embodiments, the $AUC_{0-\infty}$ when 4.5 mg of pemigatinib is administered alone is about 1100 nM·h to about 1300 nM h.

In some embodiments, the $AUC_{0-\infty}$ when 9 mg of pemigatinib is administered alone is about 250 nM·h to about 7000 nM·h.

In some embodiments, the $AUC_{0-\infty}$ when 13.5 mg of pemigatinib is administered alone is about 1700 nM·h to about 2100 nM·h. In some embodiments, the $AUC_{0-\infty}$ when 13.5 mg of pemigatinib is administered alone is about 1800 nM·h to about 2000 nM·h. In some embodiments, the $AUC_{0-\infty}$ when 13.5 mg of pemigatinib is administered alone is about 1850 nM·h to about 1950 nM·h. In some embodiments, the $AUC_{0-\infty}$ when 13.5 mg of pemigatinib is administered alone is about 1900 nM·h. In some embodiments, the $AUC_{0-\infty}$ when 13.5 mg of pemigatinib is administered alone is about 900 nM·h to about 13000 nM·h.

Also provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises the concomitant administering of a therapeutically effective amount of pemigatinib and a mild to moderate CYP3A4 inhibitor, and wherein the concomitant administration provides substantially the same therapeutic effect or adverse reaction profile of pemigatinib compared to when pemigatinib is administered alone.

Also provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises the concomitant administering of a therapeutically effective amount of pemigatinib and a mild to moderate CYP3A4 inhibitor, wherein the concomitant administering demonstrated no significant pharmacokinetic interaction.

Provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises administering a therapeutically effec-

tive amount of pemigatinib to the patient while avoiding the concomitant administration of a moderate to strong CYP3A4 inducer.

Provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of rifampin.

Provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises:

(a) determining if the patient is receiving administration of a moderate to strong CYP3A4 inducer; and

(b) administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of a moderate to strong CYP3A4 inducer.

Also provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises:

(a) discontinuing administration of a moderate to strong CYP3A4 inducer to the patient for a time period of about 5 or more half-lives of the moderate to strong CYP3A4 inducer; and

(b) administering a therapeutically effective amount of pemigatinib to the patient.

In some embodiments, the time period of discontinuing administration of a moderate to strong CYP3A4 inducer to the patient is 6 or more half-lives of the moderate to strong CYP3A4 inducer. In some embodiments, the time period of discontinuing administration of a moderate to strong CYP3A4 inducer to the patient is 7 or more half-lives of the moderate to strong CYP3A4 inducer.

Also provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises:

(a) discontinuing administration of a moderate to strong CYP3A4 inducer to the patient for a time period of about 5 or more half-lives of the moderate to strong CYP3A4 inducer; and

(b) administering a therapeutically effective amount of pemigatinib to the patient while avoiding the administration of the moderate to strong CYP3A4 inducer during treatment.

In some embodiments, the total daily amount of pemigatinib is about 9 mg to about 13.5 mg.

In some embodiments, the concomitant administration of pemigatinib and a moderate to strong CYP3A4 inducer provides an altered therapeutic effect of pemigatinib.

Also provided herein is a method of treating cancer in a patient in need thereof, wherein the method comprises orally administering a therapeutically effective amount of pemigatinib to the patient and any one or more of the following:

(a) advising the patient that moderate to strong CYP3A4 inducers should be avoided or discontinued;

(b) advising the patient that use of pemigatinib in patients being treated with moderate to strong CYP3A4 inducers is contraindicated;

(c) advising the patient that the concomitant administration of pemigatinib and moderate to strong CYP3A4 inducers can alter the therapeutic effect of pemigatinib;

(d) advising the patient that moderate to strong CYP3A4 inducers should be used with caution in patients receiving pemigatinib due to the potential for increased pemigatinib clearance;

(e) advising the patient that the concomitant administration of pemigatinib and strong CYP3A4 inducers resulted in about 6-fold to about 7-fold increase in pemigatinib clearance; or

(f) advising the patient that the concomitant administration of pemigatinib and moderate to strong CYP3A4 inducers resulted in about 6-fold to about 7-fold decrease in exposure to pemigatinib.

In some embodiments, the method further comprises advising the patient that moderate to strong CYP3A4 inducers should be avoided or discontinued. In some embodiments, the method comprises advising the patient that use of pemigatinib in patients being treated with moderate to strong CYP3A4 inducers is contraindicated. In some embodiments, the method comprises advising the patient that the concomitant administration of pemigatinib and moderate to strong CYP3A4 inducers can alter the therapeutic effect of pemigatinib. In some embodiments, the method comprises advising the patient that moderate to strong CYP3A4 inducers should be used with caution in patients receiving pemigatinib due to the potential for increased pemigatinib clearance. In some embodiments, the method comprises advising the patient that the concomitant administration of pemigatinib and strong CYP3A4 inducers resulted in about 6-fold to about 7-fold increase in pemigatinib clearance. In some embodiments, the method comprises advising the patient that the concomitant administration of pemigatinib and moderate to strong CYP3A4 inducers resulted in about 6-fold to about 7-fold decrease in exposure to pemigatinib. In some embodiments, the method comprises advising the patient that the concomitant administration of pemigatinib and moderate to strong CYP3A4 inducers resulted in about 2-fold decrease in exposure to pemigatinib. In some embodiments, the method comprises advising the patient that the concomitant administration of pemigatinib and moderate to strong CYP3A4 inducers resulted in about 7-fold decrease in exposure to pemigatinib.

Also provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises the concomitant administering a therapeutically effective amount of pemigatinib and a mild CYP3A4 inducer, and wherein the concomitant administration provides substantially the same therapeutic effect or adverse reaction profile of pemigatinib compared to when pemigatinib is administered alone.

Also provided herein is a method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises the concomitant administering of a therapeutically effective amount of pemigatinib and a mild CYP3A4 inducer, wherein the concomitant administering demonstrated no significant pharmacokinetic interaction.

Also provided herein is a method of increasing the effectiveness of pemigatinib therapy by avoiding decreased exposure to pemigatinib, in a patient in need of pemigatinib therapy that is receiving a moderate to strong CYP3A4 inducer comprising discontinuing the moderate to strong CYP3A4 inducer to decrease the levels of CYP3A4 induction, and then administering a therapeutically effective amount of pemigatinib.

In some embodiments, the time period of discontinuing administration of a moderate to strong CYP3A4 inducer is 5 or more half-lives of the moderate to strong CYP3A4 inducer. In some embodiments, the time period of discontinuing administration of a moderate to strong CYP3A4 inducer is 6 or more half-lives of the moderate to strong CYP3A4 inducer. In some embodiments, the time period of discontinuing administration of a moderate to strong CYP3A4 inducer is 7 or more half-lives of the moderate to strong CYP3A4 inducer. In some embodiments, the time

period of discontinuing administration of a moderate to strong CYP3A4 inducer is two to three weeks prior to pemigatinib administration.

Also provided herein is a method of treating a patient with pemigatinib wherein the patient is coadministering a substance that is a known strong inhibitor of CYP3A4, said method comprising adjusting administration to the patient of the substance to avoid an adverse event associated with a change in the metabolism of pemigatinib.

Also provided herein is a method of treating a patient with pemigatinib wherein the patient is coadministering a substance that is a known strong inhibitor or a known moderate to strong inducer of CYP3A4, said method comprising adjusting administration of pemigatinib or the substance to the patient to avoid an adverse reaction or a subtherapeutic outcome with pemigatinib.

In some embodiments, the adjusting administration of pemigatinib is a dosage amount suitable for the patient if the patient is not receiving a concomitant strong CYP3A4 inhibitor. In some embodiments, the adjusting administration of the substance is avoiding the coadministration of the substance that is a known moderate to strong inducer of CYP3A4.

Also provided herein is a method of avoiding an adverse event when administering pemigatinib, comprising determining that a patient in need of pemigatinib therapy is taking a substance that is a known strong inhibitor or a known moderate to strong inducer of CYP3A4; and adjusting administration to the patient of pemigatinib or the substance to avoid an adverse event associated with a change in the metabolism of pemigatinib, wherein the adjusting administration comprises ceasing to administer the substance if the substance is a moderate to strong inducer of CYP3A4 or decreasing the dosage of pemigatinib if the substance is a strong inhibitor of CYP3A4.

Also provided herein is a method of avoiding an adverse event when administering pemigatinib, comprising avoiding coadministration of pemigatinib with moderate to strong CYP3A4 inducers or strong CYP3A4 inhibitors.

Also provided herein is a method of avoiding an adverse event when administering pemigatinib, comprising avoiding concomitant administration of pemigatinib with moderate to strong CYP3A4 inducers or strong CYP3A4 inhibitors.

Also provided herein is a method of avoiding an adverse event when administering pemigatinib, comprising avoiding concomitant use of pemigatinib with moderate to strong CYP3A4 inducers or strong CYP3A4 inhibitors.

Exemplary CYP3A inhibitors (e.g., strong CYP3A4 inhibitors, moderate CYP3A4 inhibitors, and mild CYP3A4 inhibitors) are shown below in the following table.

TABLE 1

CYP3A Inhibitors	
Inhibitor	Therapeutic Class
Strong CYP3A Inhibitors	
VIEKIRA PAK	Antivirals
Indinavir/RIT	Protease inhibitors
Tipranavir/RIT	Protease inhibitors
Ritonavir	Protease inhibitors
Ketoconazole	Antifungals
Indinavir	Protease inhibitors
Troleandomycin	Antibiotics
Telaprevir	Antivirals
Danoprevir/RIT	Antivirals
Elvitegravir/RIT	Treatments of AIDS
Saquinavir/RIT	Protease inhibitors
Lopinavir/RIT	Protease inhibitors
Itraconazole	Antifungals
Voriconazole	Antifungals
Mibefradil	Calcium channel blockers
Clarithromycin	Antibiotics
Posaconazole	Antifungals
Telithromycin	Antibiotics
Grapefruit juice DS	Food products
Conivaptan	Diuretics
Nefazodone	Antidepressants
Nelfinavir	Protease inhibitors
Saquinavir	Protease inhibitors
Ribociclib	Kinase inhibitors
Idelalisib	Kinase inhibitors
Boceprevir	Antivirals
Moderate CYP3A Inhibitors	
Erythromycin	Antibiotics
Fluconazole	Antifungals
Atazanavir/RIT	Protease inhibitors
Darunavir	Protease inhibitors
Diltiazem	Calcium channel blockers
Darunavir/RIT	Protease inhibitors
Dronedarone	Antiarrhythmics
Crizotinib	Kinase inhibitors
Atazanavir	Protease inhibitors
Letermovir	Antivirals
Aprepitant	Antiemetics
Casopitant	Antiemetics
Amprenavir	Protease inhibitors
Faldaprevir	Antivirals
Imatinib	Antineoplastic agents
Verapamil	Calcium channel blockers
Netupitant	Antiemetics
Nilotinib	Kinase inhibitors
Grapefruit juice	Food products
Tofisopam	Benzodiazepines
Cyclosporine	Immunosuppressants
ACT-178882	Renin inhibitors
Ciprofloxacin	Antibiotics
Magnolia vine (*Schisandra sphenanthera*)	Herbal medications
Isavuconazole	Antifungals
Cimetidine	H-2 receptor antagonists
Mild CYP3A Inhibitors	
Tabimorelin	Hormone replacement
Amlodipine	Calcium channel blockers
Ranolazine	Cardiovascular drugs
Breviscapine	Herbal medications
Lomitapide	Other antilipemics
Fosaprepitant (IV)	Antiemetics
Seville orange (*Citrus aurantium*) juice	Food products
Amiodarone	Antiarrhythmics
Diosmin	Herbal medications
Chlorzoxazone	Muscle relaxants
Fluvoxamine	Antidepressants
Ranitidine	H-2 receptor antagonists
Goldenseal	Herbal medications
Clotrimazole	Antifungals
Tacrolimus	Immunosuppressants
Palbociclib	Kinase inhibitors
Cilostazol	Antiplatelets
Ticagrelor	Antiplatelets
Peppermint oil	Food products
Ivacaftor	Cystic fibrosis treatments
Guan Mai Ning	Herbal medications
Osilodrostat	Adrenal steroidogenesis inhibitors
Piperine	Food products
Resveratrol	Food products
Roxithromycin	Antibiotics
Suvorexant	Hypnotics - sedatives
Propiverine	Anticholinergics
Isoniazid	Antibiotics

TABLE 1-continued

CYP3A Inhibitors	
Inhibitor	Therapeutic Class
Berberine	Herbal medications
Oral contraceptives	Oral contraceptives
Delavirdine	NNRTIs
Daclatasvir	Antivirals
Simeprevir	Protease inhibitors
Atorvastatin	HMG CoA reductase inhibitors (statins)
Tolvaptan	Vasopressin antagonists
Almorexant	Hypnotics - sedatives
Evacetrapid	CETP inhibitors
Linagliptin	Dipeptidyl peptidase 4 inhibitors
Grazoprevir (ingredient of Zepatier)	Antivirals
Lacidipine	Calcium channel blockers
Cranberry juice	Food products
Pazopanib	Kinase inhibitors
Fostamatinib	Other
Everolimus	Immunosuppressants
Blueberry juice	Food products
Flibanserin	Central nervous system agents
Lapatinib	Kinase Inhibitors
Brodalumab	Immunomodulators biologics
Alprazolam	Benzodiazepines
Tong Xin Luo	Herbal medications
Glecaprevir and pibrentasvir	Antivirals
Bicalutamide	Antiandrogens
Sitaxentan	Endothelin receptor antagonists
Azithromycin	Antibiotics
Obeticholic acid	Miscellaneous agents
Ginkgo	Herbal medications
Teriflunomide	Other immunomodulators

In some embodiments, the strong CYP3A4 inhibitor is itraconazole, ketoconazole or clarithromycin. In some embodiments, the strong CYP3A4 inhibitor is itraconazole. In some embodiments, the moderate CYP3A4 inhibitor is erythromycin or diltiazem. In some embodiments, the mild CYP3A4 inhibitor is fluvoxamine. In some embodiments, the CYP3A4 inhibitor is erythromycin, diltiazem, or fluvoxamine.

Exemplary CYP3A inducers (e.g., strong CYP3A4 inducers, moderate CYP3A4 inducers, and mild CYP3A4 inducers) are shown below in the following table.

TABLE 2

Inducers	Therapeutic class
Strong CYP3A Inducers	
Rifampin	Antibiotics
Mitotane	Other Antineoplastics
Avasimibe	Other Antilipemics
Rifapentine	Antibiotics
Apalutamide	Antiandrogens
Phenytoin	Anticonvulsants
Carbamazepine	Anticonvulsants
Enzalutamide	Antiandrogens
St John's Wort extract	Herbal medications
Lumacaftor	Cystic fibrosis treatments
Rifabutin	Antibiotics
Phenobarbital	Anticonvulsants
Moderate CYP3A Inducers	
Ritonavir and St. Johns wort	None
Semagacestat	Alzheimer's treatments
Efavirenz	NNRTIs
Tipranavir and ritonavir	Protease inhibitors
Dabrafenib	Kinase inhibitors
Lesinurad	Antigout and uricosuric agents
Bosentan	Endothelin receptor antagonists
Genistein	Food products

TABLE 2-continued

Inducers	Therapeutic class
Thioridazine	Antipsychotics
Nafcillin	Antibiotics
Talviraline	NNRTIs
Lopinavir	Protease inhibitors
Modafinil	Psychostimulants
Etravirine	NNRTIs
Lersivirine	NNRTIs
Telotristat ethyl	Antidiarrheals
Mild CYP3A Inducers	
Eslicarbazepine	Anticonvulsants
Telaprevir	Antivirals
Daclatasvir and asunaprevir and beclabuvir	Antivirals
Amenamevir	Antivirals
Garlic	Food products
Bexarotene	Other antineoplastics
Sarilumab	Immunomodulators biologics
Artesunate and mefloquine	Antimalarials
Amprenavir (fosamprenavir)	Protease inhibitors
Raltegravir	HIV-integrase strand transfer inhibitors
Vemurafenib	Kinase inhibitors
Troglitazone	Thiazolidinediones
Dicloxacillin	Antibiotics
Sorafenib	Kinase inhibitors
Rufinamide	Anticonvulsants
Sirukumab	Immunomodulators biologics
Pleconaril	Antivirals
Ginseng	Herbal medications
Boceprevir	Antivirals
Sulfinpyrazone	Antigout and uricosuric agents
Ginkgo	Herbal medications
Vinblastine	Vinca alkaloids
Nevirapine	NNRTIs
Armodafmil (R-modafmil)	Psychostimulants
Ticagrelor	Anticoagulants and antiplatelets
Vicriviroc and ritonavir	Treatments of AIDS
Ritonavir	Protease inhibitors
Prednisone	Corticosteroids
Oxcarbazepine	Anticonvulsants
Danshen	Herbal medications
Clobazam	Benzodiazepines
Echinacea	Herbal medications
Ticlopidine	Anticoagulants and antiplatelets
Isavuconazole	Antifungals
Brivaracetam	Anticonvulsants
Stribild	Treatments of AIDS
Pioglitazone	Thiazolidinediones
VIEKIRA PAK	Antivirals
Dexamethasone	Corticosteroids
Terbinafine	Antifungals
Quercetin	Food products
Glycyrrhizin	Herbal medications
Aprepitant	Neurokinin-1 receptor antagonists
Pretomanib (PA-824)	Antibiotics
Safinamide	MAO-B inhibitors
Oritavancin	Antibiotics
Methylprednisolone	Corticosteroids
Topiramate	Anticonvulsants

In some embodiments, the strong CYP3A4 inducer is rifampin. In some embodiments, the moderate CYP3A4 inducer is efavirenz. In some embodiments, the mild CYP3A4 inducer is dexamethasone. In some embodiments, the CYP3A4 inducer is rifampin or efavirenz.

Pemigatinib as described herein can inhibit the activity of the FGFR enzyme. For example, pemigatinib can be used to inhibit activity of an FGFR enzyme in a cell or in an individual or patient in need of inhibition of the enzyme by administering an inhibiting amount of pemigatinib to the cell, individual, or patient.

As an FGFR inhibitor, pemigatinib is useful in the treatment of various diseases associated with abnormal expression or activity of the FGFR enzyme or FGFR ligands.

Compounds which inhibit FGFR will be useful in providing a means of preventing the growth or inducing apoptosis in tumors, particularly by inhibiting angiogenesis. It is therefore anticipated that pemigatinib will prove useful in treating or preventing proliferative disorders such as cancers. In particular tumors with activating mutants of receptor tyrosine kinases or upregulation of receptor tyrosine kinases may be particularly sensitive to the inhibitors.

In certain embodiments, the disclosure provides a method for treating a FGFR-mediated disorder in a patient in need thereof, comprising the step of administering to said patient pemigatinib, or a pharmaceutically acceptable composition thereof.

For example, pemigatinib is useful in the treatment of cancer. Example cancers include bladder cancer, breast cancer (e.g., hormone R positive, triple negative), cervical cancer, colorectal cancer, cancer of the small intestine, colon cancer, rectal cancer, cancer of the anus, endometrial cancer, gastric cancer (e.g., gastrointestinal stromal tumors), head and neck cancer (e.g., cancers of the larynx, hypopharynx, nasopharynx, oropharynx, lips, and mouth, squamous head and neck cancers), kidney cancer (e.g., renal cell carcinoma, urothelial carcinoma, sarcoma, Wilms tumor), liver cancer (e.g., hepatocellular carcinoma, cholangiocellular carcinoma, liver angiosarcoma, hepatoblastoma), lung cancer (e.g., adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, parvicellular and non-parvicellular carcinoma, bronchial carcinoma, bronchial adenoma, pleuropulmonary blastoma), ovarian cancer, prostate cancer, testicular cancer, uterine cancer, vulvar cancer, esophageal cancer, gall bladder cancer, pancreatic cancer (e.g. exocrine pancreatic carcinoma), stomach cancer, thyroid cancer, parathyroid cancer, neuroendocrine cancer (e.g., pheochromocytoma, Merkel cell cancer, neuroendocrine carcinoma), skin cancer (e.g., squamous cell carcinoma, Kaposi sarcoma, Merkel cell skin cancer), and brain cancer (e.g., astrocytoma, medulloblastoma, ependymoma, neuro-ectodermal tumors, pineal tumors).

Further example cancers include hematopoietic malignancies such as leukemia or lymphoma, multiple myeloma, chronic lymphocytic lymphoma, adult T cell leukemia, B-cell lymphoma, cutaneous T-cell lymphoma, acute myelogenous leukemia, Hodgkin's or non-Hodgkin's lymphoma, myeloproliferative neoplasms (e.g., 8p11 myeloproliferative syndrome, polycythemia vera, essential thrombocythemia, and primary myelofibrosis), myelodysplastic syndrome, chronic eosinophilic leukemia, Waldenstrom's Macroglubulinemia, hairy cell lymphoma, chronic myelogenic lymphoma, acute lymphoblastic lymphoma, AIDS-related lymphomas, and Burkitt's lymphoma.

In certain embodiments, provided herein is a method of treating myeloid/lymphoid neoplasms in a patient in need thereof. In certain embodiments, the myeloid/lymphoid neoplasms are 8p11 myeloproliferative syndrome. As used herein, the term "8p11 myeloproliferative syndrome" (EMS) is meant to refer to myeloid/lymphoid neoplasms associated with eosinophilia and abnormalities of FGFR1 or myeloid/lymphoid neoplasms (MLN) with FGFR1 rearrangement. Eight P eleven myeloproliferative syndrome is reviewed in Jackson, Courtney C., et. al. *Human Pathology,* 2010, 41, 461-476. In certain embodiments, the myeloid/lymphoid neoplasm exhibits an 8p11 translocation. In certain embodiments, the 8p11 translocation is associated with activation of FGFR1. In certain embodiments, the patient has failed at least one previous treatment for myeloid/lymphoid neoplasms (e.g., 8p11 myeloproliferative syndrome). In some embodiments, the previous treatment is surgery or radiation therapy. In some embodiments, the patient has a history of hepatitis. In some embodiments, the hepatitis is chronic hepatitis B or hepatitis C. In some embodiments, the patient does not have a history of hepatitis.

In certain embodiments, provided herein is a method of treating cancer comprising administering to a patient in need thereof a therapeutically effect amount of pemigatinib. In certain embodiments, the cancer is selected from bladder cancer, breast cancer, cervical cancer, cancer of the small intestine, colorectal cancer, endometrial cancer, gastric cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, vulvar cancer, esophageal cancer, gall bladder cancer, pancreatic cancer, thyroid cancer, skin cancer, brain cancer, leukemia, multiple myeloma, chronic lymphocytic lymphoma, adult T cell leukemia, B-cell lymphoma, acute myelogenous leukemia, Hodgkin's or non-Hodgkin's lymphoma, Waldenstrom's Macroglubulinemia, myeloproliferative neoplasms, chronic myelogenic lymphoma, acute lymphoblastic lymphoma, hairy cell lymphoma, Burkett's lymphoma, glioblastoma, melanoma, rhabdosarcoma, lymphosarcoma, and osteosarcoma.

In certain embodiments, the cancer is bladder cancer (e.g., urothelial carcinoma, squamous cell carcinoma, adenocarcinoma).

In certain embodiments, the liver cancer is cholangiocellular carcinoma (e.g., intrahepatic, hilar or perihilar, distal extrahepatic). As used herein, cholangiocellular carcinoma is the same as cholangiocarcinoma or bile duct cancer. In certain embodiments, the cholangiocarcinoma is advanced or metastatic cholangiocarcinoma. In certain embodiments, the cholangiocarcinoma is surgically unresectable. In certain embodiments, the cholangiocarcinoma is intrahepatic. In certain embodiments, the cholangiocarcinoma is extrahepatic. In certain embodiments, the cholangiocarcinoma exhibits FGFR2 tyrosine kinase fusions which define a unique molecular subtype as described in Arai, Yasuhito, et. al. *Hepatology,* 2014, 59, 1427-1434. In some embodiments, the cholangiocarcinoma is characterized by FGF/FGFR genetically altered tumors. In some embodiments, the tumors exhibit FGFR2 fusions. The FGFR2 fusion can be a translocation, interstitial deletion, or a chromosomal inversion. In some embodiments, the FGFR2 fusion is an FGFR2 translocation. The FGFR2 translocations can be selected from a group including, but not limited to, FGFR2-BICC1, FGFR2-AHCYL1, FGFR2-MACF1, FGFR2 intron 17 rearrangement. In some embodiments, the tumor exhibits FGF/FGFR alterations other than FGFR2 translocations. In some embodiments, the cholangiocarcinoma does not exhibit FGF/FGFR genetically altered tumors.

Other cancers treatable with the methods provided herein include tumors of the eye, glioblastoma, melanoma, rhabdosarcoma, lymphosarcoma, leiomyosarcoma, urothelial carcinoma (e.g., ureter, urethra, bladder, urachus), and osteosarcoma.

Pemigatinib can also be useful in the inhibition of tumor metastases.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal

response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

As used herein, the term "treating" or "treatment" refers to one or more of (1) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting further development of the pathology and/or symptomatology); and (2) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology) such as decreasing the severity of disease. In some embodiments, the term "treating" or "treatment" refers to inhibiting or ameliorating the disease.

As used herein, the term "coadministering" or "concomitant administering" refers to administering pemigatinib and one or more additional drugs (e.g., a CYP3A4 perpetrator) at or almost at the same time. For example, pemigatinib may be administered, e.g., on the same day, within a week, or within a month as the one or more additional drugs. In some embodiments, the one or more additional drugs is administered between administrations of pemigatinib.

As used herein, the term "therapy" refers to administration of a compound that is suitable for treating cancer. For example, therapy can refer to the administration of pemigatinib for treating cancer.

As used herein, the term "perpetrator" refers to a drug or compound that causes an effect on the substrate drug by inhibiting or inducing enzymes or transporters (e.g., CYP3A4). In some embodiments, the substrate drug is pemigatinib. A perpetrator can refer to, e.g., a CYP3A4 inhibitor or a CYP3A4 inducer.

As used herein, the term "C_{max}" refers to the maximum (or peak) serum concentration that a drug (e.g., pemigatinib) achieves in a specified compartment or test area of the body after the drug has been administered and before the administration of a second dose.

As used herein, the term "AUC" refers to the definite integral in a plot of drug (e.g., pemigatinib) concentration in blood plasma vs. time. The term "$AUC_{0-\infty}$." refers to the area under the concentration vs. time curve extrapolated to infinity. The term "AUC_{0-t}" refers to the area under the concentration vs. time curve up to the last measurable concentration.

As used herein, the term "$t_{1/2}$" refers to the time it takes for the serum concentration of a drug (e.g., pemigatinib) to fall to half of its original value. In other words, $t_{1/2}$ refers to the biological half-life of a drug (e.g., pemigatinib).

As used herein, and unless otherwise specified, the term "about", when used in connection with a numeric value or range of values, indicate that the value or range of values may deviate to an extent deemed reasonable by one of ordinary skill in the art. Specifically, the term "about", when used in this context, indicates that the numeric value or range of values may vary by 5%, 4%, 3%, 2%, 1%, 0.9%, 0.8%, 0.7%, 0.6%, 0.5%, 0.4%, 0.3%, 0.2% or 0.1% of the recited value or range of values.

As used herein, and unless otherwise specified, the term "substantial" or "substantially the same," when used in connection with a numeric value or range of values, indicate that the value or range of values may deviate to an extended deemed reasonable by one of ordinary skill in the art. Specifically, the term "substantially the same," when used in this context, indicates that the numeric value or range of values may vary by 20%, 10%, 15%, 5%, or 1% of the recited value or range of values. In some embodiments, the phrase "substantially the same" indicates that the numeric value or range of values may vary by 10%.

As used herein, the term "cell" is meant to refer to a cell that is in vitro, ex vivo or in vivo. In some embodiments, an ex vivo cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an in vitro cell can be a cell in a cell culture. In some embodiments, an in vivo cell is a cell living in an organism such as a mammal.

As used herein, the term "contacting" refers to the bringing together of indicated moieties in an in vitro system or an in vivo system. For example, "contacting" the FGFR enzyme with pemigatinib includes the administration of a compound described herein to an individual or patient, such as a human, having FGFR, as well as, for example, introducing pemigatinib into a sample containing a cellular or purified preparation containing the FGFR enzyme.

The phrase "pharmaceutically acceptable" is used herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, immunogenicity or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, the phrase "pharmaceutically acceptable carrier or excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. Excipients or carriers are generally safe, non-toxic and neither biologically nor otherwise undesirable and include excipients or carriers that are acceptable for veterinary use as well as human pharmaceutical use. In one embodiment, each component is "pharmaceutically acceptable" as defined herein. See, e.g., *Remington: The Science and Practice of Pharmacy,* 21st ed.; Lippincott Williams & Wilkins: Philadelphia, Pa., 2005*; Handbook of Pharmaceutical Excipients,* 6th ed.; Rowe et al., Eds.; The Pharmaceutical Press and the American Pharmaceutical Association: 2009*; Handbook of Pharmaceutical Additives,* 3rd ed.; Ash and Ash Eds.; Gower Publishing Company: 2007*; Pharmaceutical Preformulation and Formulation, 2nd ed.*; Gibson Ed.; CRC Press LLC: Boca Raton, Fla., 2009.

In some embodiments, a pharmaceutically acceptable salt of pemigatinib is used in the methods and combination therapies described herein. Salt forms of pemigatinib are described in U.S. Provisional Application No. 62/667,040.

Solid forms (e.g., crystalline forms) of pemigatinib can also be used in the methods and combination therapies described herein. Solid forms of pemigatinib, and methods of preparing solid forms of pemigatinib, are described in U.S. Provisional Application No. 62/667,166.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment (while the embodiments are intended to be combined as if written in multiply dependent form). Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination.

Combination Therapy

One or more additional pharmaceutical agents or treatment methods such as, for example, anti-viral agents, chemotherapeutics or other anti-cancer agents, immune enhanc-

ers, immunosuppressants, radiation, anti-tumor and anti-viral vaccines, cytokine therapy (e.g., IL2, GM-CSF, etc.), and/or tyrosine kinase inhibitors can be used in combination with pemigatinib for treatment of FGFR-associated diseases, disorders or conditions, or diseases or conditions as described herein. The agents can be combined with the present compounds in a single dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

Pemigatinib can be used in combination with one or more other kinase inhibitors for the treatment of diseases, such as cancer, that are impacted by multiple signaling pathways. For example, a combination can include one or more inhibitors of the following kinases for the treatment of cancer: Akt1, Akt2, Akt3, TGF-βR, Pim, PKA, PKG, PKC, CaM-kinase, phosphorylase kinase, MEKK, ERK, MAPK, mTOR, EGFR, HER2, HER3, HER4, INS-R, IGF-1R, IR-R, PDGFαR, PDGFβR, CSFIR, KIT, FLK-II, KDR/FLK-1, FLK-4, fit-1, FGFR1, FGFR2, FGFR3, FGFR4, c-Met, Ron, Sea, TRKA, TRKB, TRKC, FLT3, VEGFR/Flt2, Flt4, EphA1, EphA2, EphA3, EphB2, EphB4, Tie2, Src, Fyn, Lck, Fgr, Btk, Fak, SYK, FRK, JAK, ABL, ALK and B-Raf Additionally, pemigatinib can be combined with inhibitors of kinases associated with the PIK3/Akt/mTOR signaling pathway, such as PI3K, Akt (including Akt1, Akt2 and Akt3) and mTOR kinases.

In some embodiments, pemigatinib can be used in combination with one or more inhibitors of the enzyme or protein receptors such as HPK1, SBLB, TUT4, A2A/A2B, CD47, CDK2, STING, ALK2, LIN28, ADAR1, MAT2a, RIOK1, HDAC8, WDR5, SMARCA2, and DCLK1 for the treatment of diseases and disorders. Exemplary diseases and disorders include cancer, infection, inflammation and neurodegenerative disorders.

In some embodiments, pemigatinib can be used in combination with a therapeutic agent that targets an epigenetic regulator. Examples of epigenetic regulators include bromodomain inhibitors, the histone lysine methyltransferases, histone arginine methyl transferases, histone demethylases, histone deacetylases, histone acetylases, and DNA methyltransferases. Histone deacetylase inhibitors include, e.g., vorinostat.

For treating cancer and other proliferative diseases, pemigatinib can be used in combination with targeted therapies, including JAK kinase inhibitors (Ruxolitinib, additional JAK1/2 and JAK1-selective, baricitinib or INCB39110), Pim kinase inhibitors (e.g., INCB53914), PI3 kinase inhibitors including PI3K-delta selective and broad spectrum PI3K inhibitors (e.g., INCB50465 and INCB54707), PI3K-gamma inhibitors such as PI3K-gamma selective inhibitors, MEK inhibitors, CSF1R inhibitors, TAM receptor tyrosine kinases inhibitors (Tyro-3, Axl, and Mer; e.g., INCB81776), angiogenesis inhibitors, interleukin receptor inhibitors, Cyclin Dependent kinase inhibitors, BRAF inhibitors, mTOR inhibitors, proteasome inhibitors (Bortezomib, Carfilzomib), HDAC-inhibitors (panobinostat, vorinostat), DNA methyl transferase inhibitors, dexamethasone, bromo and extra terminal family members inhibitors (for example, bromodomain inhibitors or BET inhibitors, such as INCB54329 or INCB57643), LSD1 inhibitors (e.g., INCB59872 or INCB60003), arginase inhibitors (e.g., INCB1158), indoleamine 2,3-dioxygenase inhibitors (e.g., epacadostat, NLG919 or BMS-986205), and PARP inhibitors (e.g., olaparib or rucaparib).

For treating cancer and other proliferative diseases, pemigatinib can be used in combination with chemotherapeutic agents, agonists or antagonists of nuclear receptors, or other anti-proliferative agents. Pemigatinib can also be used in combination with a medical therapy such as surgery or radiotherapy, e.g., gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes. Examples of suitable chemotherapeutic agents include any of: abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, anastrozole, arsenic trioxide, asparaginase, azacitidine, baricitinib, bendamustine, bevacizumab, bexarotene, bleomycin, bortezombi, bortezomib, busulfan intravenous, busulfan oral, calusterone, capecitabine, carboplatin, carmustine, cetuximab, chlorambucil, cisplatin, cladribine, clofarabine, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, dalteparin sodium, dasatinib, daunorubicin, decitabine, denileukin, denileukin diftitox, dexrazoxane, docetaxel, doxorubicin, dromostanolone propionate, eculizumab, epirubicin, erlotinib, estramustine, etoposide phosphate, etoposide, exemestane, fentanyl citrate, filgrastim, floxuridine, fludarabine, fluorouracil, fulvestrant, gefitinib, gemcitabine, gemtuzumab ozogamicin, goserelin acetate, histrelin acetate, ibritumomab tiuxetan, idarubicin, ifosfamide, imatinib mesylate, interferon alfa 2a, irinotecan, lapatinib ditosylate, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, mecloretharnine, megestrol acetate, melphalan, mercaptopurine, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone phenpropionate, nelarabine, niraparib, nofetumomab, olaparib, oxaliplatin, paclitaxel, pamidronate, panobinostat, panitumumab, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, procarbazine, quinacrine, rasburicase, rituximab, rucaparib, ruxolitinib, sorafenib, streptozocin, sunitinib, sunitinib maleate, tamoxifen, temozolomide, teniposide, testolactone, thalidomide, thioguanine, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, vorinostat, veliparib, talazoparib and zoledronate.

In some embodiments, pemigatinib can be used in combination with immune checkpoint inhibitors. Exemplary immune checkpoint inhibitors include inhibitors against immune checkpoint molecules such as CD27, CD28, CD40, CD122, CD96, CD73, CD47, OX40, GITR, CSF1R, JAK, PI3K delta, PI3K gamma, TAM, arginase, CD137 (also known as 4-1BB), ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, LAG3 (e.g., INCAGN2385), TIM3 (e.g., INCB2390), VISTA, PD-1, PD-L1 and PD-L2. In some embodiments, the immune checkpoint molecule is a stimulatory checkpoint molecule selected from CD27, CD28, CD40, ICOS, OX40 (e.g., INCAGN1949), GITR (e.g., INCAGN1876) and CD137. In some embodiments, the immune checkpoint molecule is an inhibitory checkpoint molecule selected from A2AR, B7-H3, B7-H4, BTLA, CTLA-4, IDO, KIR, LAG3, PD-1, TIM3, and VISTA. In some embodiments, the compounds provided herein can be used in combination with one or more agents selected from KIR inhibitors, TIGIT inhibitors, LAIR1 inhibitors, CD160 inhibitors, 2B4 inhibitors and TGFR beta inhibitors.

In some embodiments, the inhibitor of an immune checkpoint molecule is anti-PD1 antibody, anti-PD-L1 antibody, or anti-CTLA-4 antibody.

In some embodiments, the inhibitor of an immune checkpoint molecule is a small molecule PD-L1 inhibitor. In some embodiments, the small molecule PD-L1 inhibitor has an IC50 less than 1 μM, less than 100 nM, less than 10 nM or less than 1 nM in a PD-L1 assay described in US Patent Publication Nos. US 20170107216, US 20170145025, US 20170174671, US 20170174679, US 20170320875, US

20170342060, US 20170362253, and US 20180016260, each of which is incorporated by reference in its entirety for all purposes.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-1, e.g., an anti-PD-1 monoclonal antibody. In some embodiments, the anti-PD-1 monoclonal antibody is MGA012, nivolumab, pembrolizumab (also known as MK-3475), pidilizumab, SHR-1210, PDR001, ipilumimab or AMP-224. In some embodiments, the anti-PD-1 monoclonal antibody is nivolumab or pembrolizumab. In some embodiments, the anti-PD1 antibody is nivolumab. In some embodiments, the anti-PD1 antibody is pembrolizumab. In some embodiments, the anti-PD-1 monoclonal antibody is MGA012. In some embodiments, the anti-PD1 antibody is SHR-1210. Other anti-cancer agent(s) include antibody therapeutics such as 4-1BB (e.g. urelumab, utomilumab.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of PD-L1, e.g., an anti-PD-L1 monoclonal antibody. In some embodiments, the anti-PD-L1 monoclonal antibody is BMS-935559, MEDI4736, MPDL3280A (also known as RG7446), or MSB0010718C. In some embodiments, the anti-PD-L1 monoclonal antibody is MPDL3280A or MEDI4736. In some embodiments, the PD-L1 inhibitor is INCB086550.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of CTLA-4, e.g., an anti-CTLA-4 antibody. In some embodiments, the anti-CTLA-4 antibody is ipilimumab.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of LAG3, e.g., an anti-LAG3 antibody. In some embodiments, the anti-LAG3 antibody is BMS-986016 or LAG525.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of GITR, e.g., an anti-GITR antibody. In some embodiments, the anti-GITR antibody is TRX518 or MK-4166.

In some embodiments, the inhibitor of an immune checkpoint molecule is an inhibitor of OX40, e.g., an anti-OX40 antibody or OX40L fusion protein. In some embodiments, the anti-OX40 antibody is MEDI0562. In some embodiments, the OX40L fusion protein is MEDI6383.

In some embodiments, pemigatinib can be used in combination with one or more agents for the treatment of diseases such as cancer. In some embodiments, the agent is an alkylating agent, a proteasome inhibitor, a corticosteroid, or an immunomodulatory agent. Examples of an alkylating agent include cyclophosphamide (CY), melphalan (MEL), and bendamustine. In some embodiments, the proteasome inhibitor is carfilzomib. In some embodiments, the corticosteroid is dexamethasone (DEX). In some embodiments, the immunomodulatory agent is lenalidomide (LEN) or pomalidomide (POM).

Suitable antiviral agents contemplated for use in combination with pemigatinib can comprise nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors and other antiviral drugs.

Example suitable NRTIs include zidovudine (AZT); didanosine (ddI); zalcitabine (ddC); stavudine (d4T); lamivudine (3TC); abacavir (1592U89); adefovir dipivoxil [bis(POM)-PMEA]; lobucavir (BMS-180194); BCH-10652; emitricitabine [(−)-FTC]; beta-L-FD4 (also called beta-L-D4C and named beta-L-2',3'-dicleoxy-5-fluoro-cytidene); DAPD, ((−)-beta-D-2,6-diamino-purine dioxolane); and lodenosine (FddA). Typical suitable NNRTIs include nevirapine (BI-RG-587); delaviradine (BHAP, U-90152); efavirenz (DMP-266); PNU-142721; AG-1549; MKC-442 (1-(ethoxy-methyl)-5-(1-methylethyl)-6-(phenylmethyl)-(2,4 (1H,3H)-pyrimidinedione); and (+)-calanolide A (NSC-675451) and B. Typical suitable protease inhibitors include saquinavir (Ro 31-8959); ritonavir (ABT-538); indinavir (MK-639); nelfnavir (AG-1343); amprenavir (141W94); lasinavir (BMS-234475); DMP-450; BMS-2322623; ABT-378; and AG-1 549. Other antiviral agents include hydroxyurea, ribavirin, IL-2, IL-12, pentafuside and Yissum Project No. 11607.

Suitable agents for use in combination with pemigatinib for the treatment of cancer include chemotherapeutic agents, targeted cancer therapies, immunotherapies or radiation therapy. Pemigatinib may be effective in combination with anti-hormonal agents for treatment of breast cancer and other tumors. Suitable examples are anti-estrogen agents including but not limited to tamoxifen and toremifene, aromatase inhibitors including but not limited to letrozole, anastrozole, and exemestane, adrenocorticosteroids (e.g. prednisone), progestins (e.g. megastrol acetate), and estrogen receptor antagonists (e.g. fulvestrant). Suitable anti-hormone agents used for treatment of prostate and other cancers may also be combined with pemigatinib. These include anti-androgens including but not limited to flutamide, bicalutamide, and nilutamide, luteinizing hormone-releasing hormone (LHRH) analogs including leuprolide, goserelin, triptorelin, and histrelin, LHRH antagonists (e.g. degarelix), androgen receptor blockers (e.g. enzalutamide) and agents that inhibit androgen production (e.g. abiraterone).

Pemigatinib may be combined with or in sequence with other agents against membrane receptor kinases especially for patients who have developed primary or acquired resistance to the targeted therapy. These therapeutic agents include inhibitors or antibodies against EGFR, Her2, VEGFR, c-Met, Ret, IGFR1, or Flt-3 and against cancer-associated fusion protein kinases such as Bcr-Abl and EML4-Alk. Inhibitors against EGFR include gefitinib and erlotinib, and inhibitors against EGFR/Her2 include but are not limited to dacomitinib, afatinib, lapitinib and neratinib. Antibodies against the EGFR include but are not limited to cetuximab, panitumumab and necitumumab. Inhibitors of c-Met may be used in combination with FGFR inhibitors. These include onartumzumab, tivantnib, and INC-280. Agents against Abl (or Bcr-Abl) include imatinib, dasatinib, nilotinib, and ponatinib and those against Alk (or EML4-ALK) include crizotinib.

Angiogenesis inhibitors may be efficacious in some tumors in combination with FGFR inhibitors. These include antibodies against VEGF or VEGFR or kinase inhibitors of VEGFR. Antibodies or other therapeutic proteins against VEGF include bevacizumab and aflibercept. Inhibitors of VEGFR kinases and other anti-angiogenesis inhibitors include but are not limited to sunitinib, sorafenib, axitinib, cediranib, pazopanib, regorafenib, brivanib, and vandetanib

Activation of intracellular signaling pathways is frequent in cancer, and agents targeting components of these pathways have been combined with receptor targeting agents to enhance efficacy and reduce resistance. Examples of agents that may be combined with pemigatinib include inhibitors of the PI3K-AKT-mTOR pathway, inhibitors of the Raf-MAPK pathway, inhibitors of JAK-STAT pathway, and inhibitors of protein chaperones and cell cycle progression.

Agents against the PI3 kinase include but are not limited topilaralisib, idelalisib, buparlisib. Inhibitors of mTOR such as rapamycin, sirolimus, temsirolimus, and everolimus may be combined with FGFR inhibitors. Other suitable examples

include but are not limited to vemurafenib and dabrafenib (Raf inhibitors) and trametinib, selumetinib and GDC-0973 (MEK inhibitors). Inhibitors of one or more JAKs (e.g., ruxolitinib, baricitinib, tofacitinib), Hsp90 (e.g., tanespimycin), cyclin dependent kinases (e.g., palbociclib), HDACs (e.g., panobinostat), PARP (e.g., olaparib), and proteasomes (e.g., bortezomib, carfilzomib) can also be combined with pemigatinib. In some embodiments, the JAK inhibitor is selective for JAK1 over JAK2 and JAK3.

Other suitable agents for use in combination with pemigatinib include chemotherapy combinations such as platinum-based doublets used in lung cancer and other solid tumors (cisplatin or carboplatin plus gemcitabine; cisplatin or carboplatin plus docetaxel; cisplatin or carboplatin plus paclitaxel; cisplatin or carboplatin plus pemetrexed) or gemcitabine plus paclitaxel bound particles (Abraxane®).

Suitable chemotherapeutic or other anti-cancer agents include, for example, alkylating agents (including, without limitation, nitrogen mustards, ethylenimine derivatives, alkyl sulfonates, nitrosoureas and triazenes) such as uracil mustard, chlormethine, cyclophosphamide (Cytoxan™), ifosfamide, melphalan, chlorambucil, pipobroman, triethylene-melamine, triethylenethiophosphoramine, busulfan, carmustine, lomustine, streptozocin, dacarbazine, and temozolomide.

Other suitable agents for use in combination with pemigatinib include: dacarbazine (DTIC), optionally, along with other chemotherapy drugs such as carmustine (BCNU) and cisplatin; the "Dartmouth regimen," which consists of DTIC, BCNU, cisplatin and tamoxifen; a combination of cisplatin, vinblastine, and DTIC; or temozolomide. Pemigatinib may also be combined with immunotherapy drugs, including cytokines such as interferon alpha, interleukin 2, and tumor necrosis factor (TNF) in.

Suitable chemotherapeutic or other anti-cancer agents include, for example, antimetabolites (including, without limitation, folic acid antagonists, pyrimidine analogs, purine analogs and adenosine deaminase inhibitors) such as methotrexate, 5-fluorouracil, floxuridine, cytarabine, 6-mercaptopurine, 6-thioguanine, fludarabine phosphate, pentostatine, and gemcitabine.

Suitable chemotherapeutic or other anti-cancer agents further include, for example, certain natural products and their derivatives (for example, *vinca* alkaloids, antitumor antibiotics, enzymes, lymphokines and epipodophyllotoxins) such as vinblastine, vincristine, vindesine, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, ara-C, paclitaxel (TAXOL™), mithramycin, deoxycoformycin, mitomycin-C, L-asparaginase, interferons (especially IFN-α), etoposide, and teniposide.

Other cytotoxic agents include navelbene, CPT-11, anastrazole, letrazole, capecitabine, reloxafine, cyclophosphamide, ifosamide, and droloxafine.

Also suitable are cytotoxic agents such as epidophyllotoxin; an antineoplastic enzyme; a topoisomerase inhibitor; procarbazine; mitoxantrone; platinum coordination complexes such as cis-platin and carboplatin; biological response modifiers; growth inhibitors; antihormonal therapeutic agents; leucovorin; tegafur; and haematopoietic growth factors.

Other anti-cancer agent(s) include antibody therapeutics such as trastuzumab (Herceptin), antibodies to costimulatory molecules such as CTLA-4, 4-1BB, PD-L1 and PD-1 antibodies, or antibodies to cytokines (IL-10, TGF-β, etc.).

Other anti-cancer agents also include those that block immune cell migration such as antagonists to chemokine receptors, including CCR2 and CCR4.

Other anti-cancer agents also include those that augment the immune system such as adjuvants or adoptive T cell transfer.

Anti-cancer vaccines include dendritic cells, synthetic peptides, DNA vaccines and recombinant viruses.

Methods for the safe and effective administration of most of these chemotherapeutic agents are known to those skilled in the art. In addition, their administration is described in the standard literature. For example, the administration of many of the chemotherapeutic agents is described in the "Physicians' Desk Reference" (PDR, e.g., 1996 edition, Medical Economics Company, Montvale, N.J.), the disclosure of which is incorporated herein by reference as if set forth in its entirety.

Pharmaceutical Formulations and Dosage Forms

When employed as pharmaceuticals, pemigatinib as described herein can be administered in the form of pharmaceutical compositions which refers to a combination of pemigatinib as described herein, and at least one pharmaceutically acceptable carrier. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal, intranasal, epidermal and transdermal), ocular, oral or parenteral. Methods for ocular delivery can include topical administration (eye drops), subconjunctival, periocular or intravitreal injection or introduction by balloon catheter or ophthalmic inserts surgically placed in the conjunctival sac. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal, or intramuscular injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable.

This disclosure also includes pharmaceutical compositions which contain, as the active ingredient, pemigatinib in combination with one or more pharmaceutically acceptable carriers. In making the compositions described herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, the active compound can be milled to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it can be milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size can be adjusted

by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions described herein can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions can be formulated in a unit dosage form, each dosage containing from about 4 to about 5 mg, or about 4.5 mg, of the active ingredient. In some embodiments, the unit dosage form contains about 9 mg of the active ingredient. In some embodiments, the unity dosage form contains about 13.5 mg of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid pre-formulation composition containing a homogeneous mixture of pemigatinib. When referring to these pre-formulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid pre-formulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present disclosure.

In some embodiments, pemigatinib is administered orally. In some embodiments, pemigatinib is administered once daily. In some embodiments, pemigatinib is administered in a daily dose of about 5 mg to about 20 mg. In some embodiments, pemigatinib is administered in a daily dose of about 10 mg to about 15 mg. In some embodiments, pemigatinib is administered in a daily dose of about 13.5 mg. In some embodiments, pemigatinib is administered as a tablet. In some embodiments, the tablet comprises about 0.5 mg to about 10 mg of pemigatinib. In some embodiments, the tablet comprises about 0.5 mg to about 5 mg pemigatinib. In some embodiments, the tablet comprises about 2 mg, about 4.5 mg, about 9 mg, about 13.5 mg, or about 18 mg of pemigatinib. In some embodiments, the tablet comprises about 0.5 mg of pemigatinib. In some embodiments, the tablet comprises about 2 mg of pemigatinib. In some embodiments, the tablet comprises about 4.5 mg of pemigatinib. In some embodiments, the tablet comprises about 9 mg of pemigatinib. In some embodiments, the tablet comprises about 13.5 mg of pemigatinib. In some embodiments, the tablet comprises about 18 mg of pemigatinib.

The tablets or pills of the present disclosure can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the pemigatinib, or compositions as described herein can be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described supra. In some embodiments, the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in can be nebulized by use of inert gases. Nebulized solutions may be breathed directly from the nebulizing device or the nebulizing device can be attached to a face masks tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions can be administered orally or nasally from devices which deliver the formulation in an appropriate manner.

The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

The therapeutic dosage of pemigatinib can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of pemigatinib in a pharmaceutical composition can vary

depending upon a number of factors including dosage, chemical characteristics (e.g., hydrophobicity), and the route of administration. For example, pemigatinib can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from in vitro or animal model test systems.

Pemigatinib can also be formulated in combination with one or more additional active ingredients which can include any pharmaceutical agent such as anti-viral agents, vaccines, antibodies, immune enhancers, immune suppressants, anti-inflammatory agents and the like.

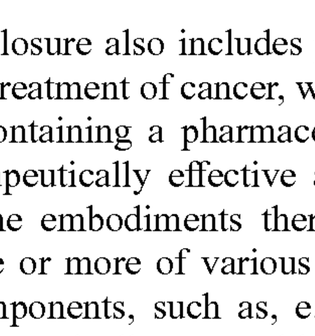
Kits

The present disclosure also includes pharmaceutical kits useful, e.g., in the treatment of cancer, which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of pemigatinib, or any of the embodiments thereof. Such kits can further include one or more of various conventional pharmaceutical kit components, such as, e.g., containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. In some embodiments, the kit further comprises a CYP3A4 inhibitor. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

EXAMPLES

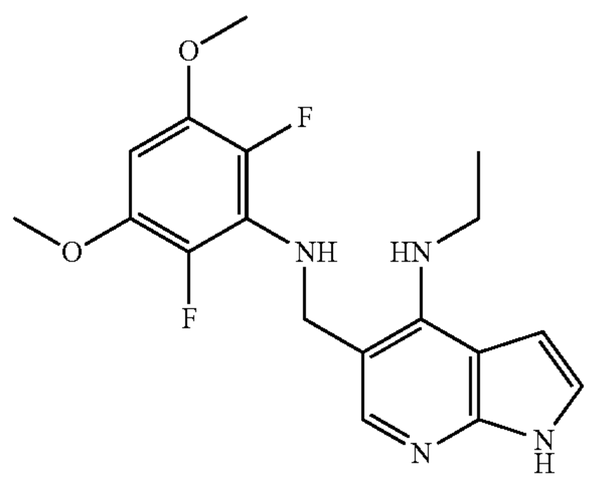
Example 1. Synthesis of Pemigatinib

Step 1: 4-(ethylamino)-1H-pyrrolo[2,3-b]pyridine-5-carbaldehyde



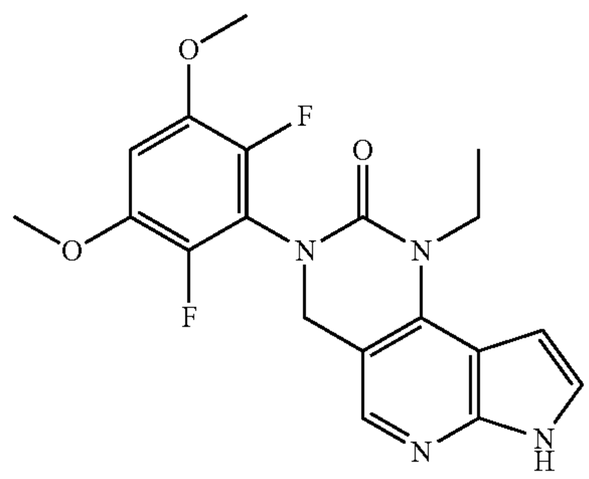
A mixture of 4-chloro-1H-pyrrolo[2,3-b]pyridine-5-carbaldehyde (CAS #958230-19-8, Lakestar Tech, Lot: 124-132-29: 3.0 g, 17 mmol) and ethylamine (10M in water, 8.3 mL, 83 mmol) in 2-methoxyethanol (20 mL, 200 mmol) was heated to 130° C. and stirred overnight. The mixture was cooled to room temperature then concentrated under reduced pressure. The residue was treated with 1N HCl (30 mL) and stirred at room temperature for 1 h then neutralized with saturated $NaHCO_3$ aqueous solution. The precipitate was collected via filtration then washed with water and dried to provide the desired product (2.9 g, 92%). LC-MS calculated for $C_{10}H_{12}N_3O$ $[M+H]^+$ m/z: 190.1; found: 190.1.

Step 2: 5-{[(2,6-difluoro-3,5-dimethoxyphenyl)amino]methyl}-N-ethyl-1H-pyrrolo[2,3-b]pyridin-4-amine



A mixture of 4-(ethylamino)-1H-pyrrolo[2,3-b]pyridine-5-carbaldehyde (7.0 g, 37 mmol), 2,6-difluoro-3,5-dimethoxyaniline (9.1 g, 48 mmol) and [(1S)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]methanesulfonic acid (Aldrich, cat #21360: 2 g, 7 mmol) in xylenes (250 mL) was heated to reflux with azeotropic removal of water using Dean-Stark for 2 days at which time LC-MS showed the reaction was complete. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in tetrahydrofuran (500 mL) and then 2.0 M lithium tetrahydroaluminate in THF (37 mL, 74 mmol) was added slowly and the resulting mixture was stirred at 50° C. for 3 h then cooled to room temperature. The reaction was quenched by addition of water, 15% aqueous NaOH and water. The mixture was filtered and washed with THF. The filtrate was concentrated and the residue was washed with CH_2Cl_2 and then filtered to get the pure product (11 g, 82%). LC-MS calculated for $C_{18}H_{21}F_2N_4O_2[M+H]^+$ m/z: 363.2; found: 363.1.

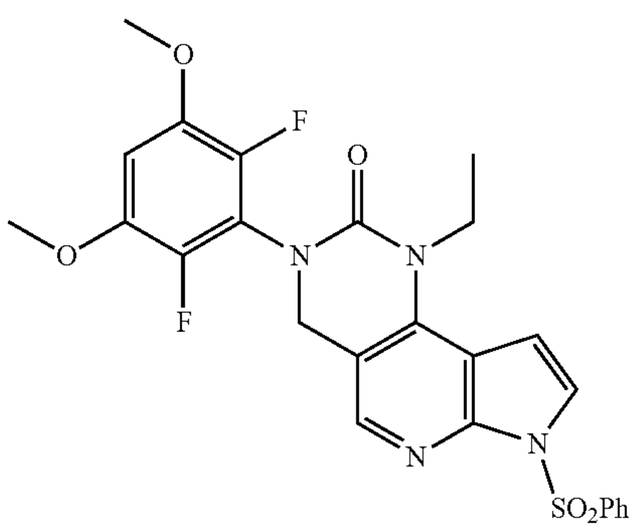
Step 3: 3-(2,6-Difluoro-3,5-dimethoxyphenyl)-1-ethyl-1,3,4,7-tetrahydro-2H-pyrrolo[3',2':5,6]pyrido[4,3-d]pyrimidin-2-one



A solution of triphosgene (5.5 g, 18 mmol) in tetrahydrofuran (30 mL) was added slowly to a mixture of 5-{[(2,6-difluoro-3,5-dimethoxyphenyl)amino]methyl}-N-ethyl-1H-pyrrolo[2,3-b]pyridin-4-amine (5.6 g, 15 mmol) in tetrahydrofuran (100 mL) at 0° C. and then the mixture was stirred at room temperature for 6 h. The mixture was cooled to 0° C. and then 1.0 M sodium hydroxide in water (100 mL,

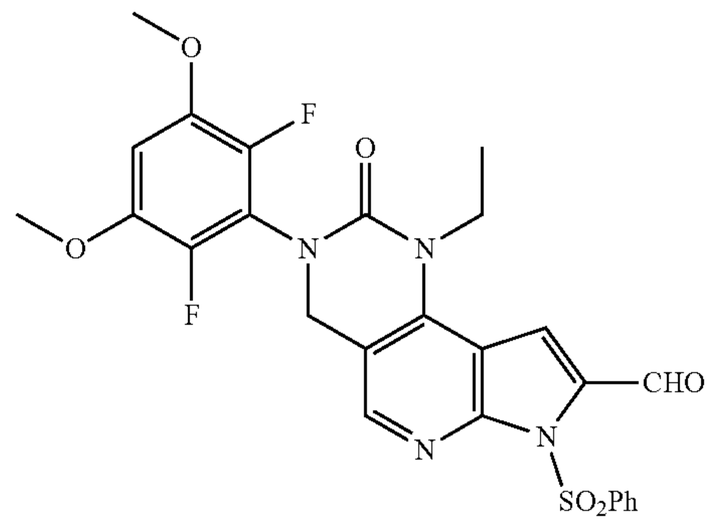
100 mmol) was added slowly. The reaction mixture was stirred at room temperature overnight and the formed precipitate was collected via filtration, washed with water, and then dried to provide the first batch of the purified desired product. The organic layer in the filtrate was separated and the aqueous layer was extracted with methylene chloride. The combined organic layer was concentrated and the residue was triturated with methylene chloride then filtered and dried to provide another batch of the product (total 5.5 g, 92%). LC-MS calculated for $C_{19}H_{19}F_2N_4O_3[M+H]^+$ m/z: 389.1; found: 389.1.

Step 4: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(phenylsulfonyl)-1,3,4,7-tetrahydro-2H-pyrrolo[3',2':5,6]pyrido[4,3-d]pyrimidin-2-one



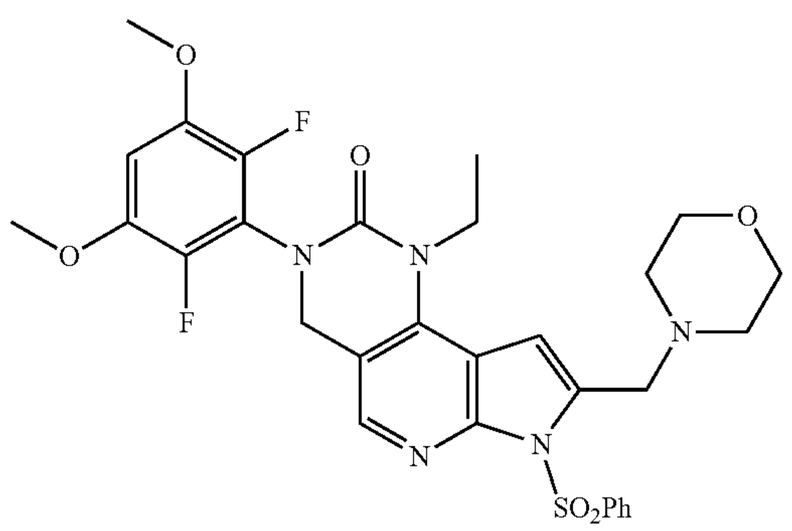
To a solution of 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-1,3,4,7-tetrahydro-2H-pyrrolo[3',2':5,6]pyrido[4,3-d]pyrimidin-2-one (900 mg, 2.32 mmol) in N,N-dimethylformamide (20 mL) cooled to 0° C. was added sodium hydride (185 mg, 4.63 mmol, 60 wt % in mineral oil). The resulting mixture was stirred at 0° C. for 30 min then benzenesulfonyl chloride (0.444 mL, 3.48 mmol) was added. The reaction mixture was stirred at 0° C. for 1.5 h at which time LC-MS showed the reaction completed to the desired product. The reaction was quenched with saturated NH_4Cl solution and diluted with water. The white precipitate was collected via filtration then washed with water and hexanes, dried to afford the desired product (1.2 g, 98%) as a white solid which was used in the next step without further purification. LC-MS calculated for $C_{25}H_{23}F_2N_4O_5S$ $[M+H]^+$ m/z: 529.1; found: 529.1.

Step 5: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-7-(phenylsulfonyl)-2,3,4,7-tetrahydro-1H-pyrrolo[3',2':5,6]pyrido[4,3-d]pyrimidine-8-carbaldehyde



To a solution of 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-7-(phenylsulfonyl)-1,3,4,7-tetrahydro2H-pyrrolo[3',2': 5,6]pyrido[4,3-d]pyrimidin-2-one (1.75 g, 3.31 mmol) in tetrahydrofuran (80 mL) at −78° C. was added freshly prepared lithium diisopropylamide (1M in tetrahydrofuran (THF), 3.48 mL, 3.48 mmol). The resulting mixture was stirred at −78° C. for 30 min then N,N-dimethylformamide (1.4 mL, 18 mmol) was added slowly. The reaction mixture was stirred at −78° C. for 30 min then quenched with water and extracted with EtOAc. The organic extracts were combined then washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography eluted with 0 to 20% EtOAc in DCM to give the desired product as a white solid (1.68 g, 91%). LC-MS calculated for $C_{26}H_{23}F_2N_4O_6S$ $(M+H)^+$ m/z: 557.1; found: 556.9.

Step 6: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-(morpholin-4-ylmethyl)-7-(phenylsulfonyl)-1,3,4,7-tetrahydro-2H-pyrrolo[3',2':5,6]pyrido[4,3-d]pyrimidin-2-one



To a solution 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-2-oxo-7-(phenylsulfonyl)-2,3,4,7-tetrahydro-1H-pyrrolo[3',2': 5,6]pyrido[4,3-d]pyrimidine-8-carbaldehyde (1.73 g, 3.11 mmol) in dichloromethane (50 mL) was added morpholine (0.95 mL, 11 mmol), followed by acetic acid (2 mL, 30 mmol). The resulting yellow solution was stirred at room temperature overnight then sodium triacetoxyborohydride (2.3 g, 11 mmol) was added. The mixture was stirred

at room temperature for 3 h at which time LC-MS showed the reaction went to completion to the desired product. The reaction was quenched with saturated $NaHCO_3$ then extracted with ethyl acetate (EtOAc). The organic extracts were combined then washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography eluted with 0 to 40% EtOAc in DCM to give the desired product as a yellow solid (1.85 g, 95%). LC-MS calculated for $C_{30}H_{32}F_2N_5O_6S$ $(M+H)^+$ m/z: 628.2; found: 628.0.

Step 7: 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-(morpholin-4-ylmethyl)-1,3,4,7-tetrahydro-2H-pyrrolo[3',2': 5,6]pyrido[4,3-d]pyrimidin-2-one (pemigatinib)

To a solution of 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-(morpholin-4-ylmethyl)-7-(phenylsulfonyl)-1,3,4,7-tetrahydro-2H-pyrrolo[3',2': 5,6]pyrido[4,3-d]pyrimidin-2-one (1.5 g, 2.4 mmol) in tetrahydrofuran (40 mL) was added tetra-n-butylammonium fluoride (1M in THF, 7.2 mL, 7.2 mmol). The resulting solution was stirred at 50° C. for 1.5 h then cooled to room temperature and quenched with water. The mixture was extracted with dichloromethane (DCM) and the organic extracts were combined then washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography eluted with 0 to 10% MeOH in DCM to give the desired product as a white solid, which was further purified by prep HPLC (pH=2, acetonitrile/H_2O). LC-MS calculated for $C_{24}H_{28}F_2N_5O_4$ $(M+H)^+$ m/z: 488.2; found: 488.0. ^1H NMR (500 MHz, DMSO) δ 12.09 (s, 1H), 8.06 (s, 1H), 7.05 (t, J=8.1 Hz, 1H), 6.87 (s, 1H), 4.78 (s, 2H), 4.50 (s, 2H), 4.17 (q, J=6.8 Hz, 2H), 3.97 (br, 2H), 3.89 (s, 6H), 3.65 (br, 2H), 3.37 (br, 2H), 3.15 (br, 2H), 1.37 (t, J=6.8 Hz, 3H).

Example A. Study to Assess the Effect of Itraconazole and Rifampin on Pemigatinib Pharmacokinetics when Administered Orally in Healthy Patients

This Example describes an ongoing Phase 1 clinical study to assess the effect of multiple doses of itraconazole, a potent CYP3A4 inhibitor, or rifampin, a potent CYP3A4 inducer, on the single-dose pharmacokinetics (e.g., C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of pemigatinib.

In addition, this study also evaluates the safety and tolerability of pemigatinib when administered alone or in combination with itraconazole or rifampin. Safety and tolerability is assessed by monitoring adverse events, vital signs, physical examinations, 12-lead ECGs, and clinical laboratory blood and urine sample assessments. Pharmacokinetic endpoints include t_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, CL/F, and V_z/F.

The study is an open-label, fixed sequence, drug-drug interaction (DDI) study to assess the effect of multiple doses of itraconazole or rifampin on the single-dose PK of pemigatinib. Thirty-six healthy participants are divided into 2 cohorts of 18 participants. The study enrolls healthy adult participants aged 18 to 55 years.

In the first cohort, Cohort 1, participants receive each of the following treatments in succession:

- Day 1: pemigatinib 4.5 mg (4.5 mg×1) single dose administered orally in the fasted state;
- Days 4 through 7: Itraconazole 200 mg (100 mg×2) QD in the fed state (4 doses);
- Day 8: pemigatinib 4.5 mg (4.5 mg xl) single dose and itraconazole 200 mg (100 mg×2) single dose in the fasted state; and
- Day 9 through 11: Itraconazole 200 mg (100 mg×2) single dose in the fed state.

Vital signs (oral temperature; respiratory rate; automated, seated blood pressure; and pulse) are obtained at screening, check-in, and follow-up; at 0 hour (predose) on Days 1 and 8; and at approximately 1, 2, 3, 6, and 24 hours after the morning dose on Day 4 and Day 9. Clinical safety laboratory assessments are performed at screening; on Days −1, 2, 5, 9, 10, and 11; and at follow-up. A serum pregnancy is obtained at screening and follow-up. A urine pregnancy test is obtained at check-in for each visit for all women. On Day 8, a 12-lead ECG is performed predose, 2 hours postdose, and approximately 24 hours postdose. On other days, 12-lead ECGs are performed only at predose.

Pemigatinib is administered as follows: Participants enter the CRU on Day −1 and remain in the clinic until discharged on Day 12. They receive a single oral dose of pemigatinib 4.5 mg under fasted conditions on Day 1. On Days 4 through 7, they receive itraconazole 200 mg QD under fed conditions. On Day 8, participants receive single doses of pemigatinib 4.5 mg and itraconazole 200 mg under fasted conditions. On Days 9 through 11, participants will receive itraconazole 200 mg QD dose under fed conditions. Participants are discharged from the unit on Day 12.

In the second cohort, Cohort 2, participants receive each of the following treatments in succession:

- Day 1: pemigatinib 13.5 mg (4.5 mg×3) single dose administered orally in the fasted state;
- Days 4 through 10: Rifampin 600 mg (300 mg×2) QD in the fasted state (7 doses);
- Day 11: pemigatinib 13.5 mg (4.5 mg×3) single dose and rifampin 600 mg (300 mg×2) single dose in the fasted state;
- Day 12: Rifampin 600 mg (300 mg×2) QD in the fasted state.

Vital signs (oral temperature; respiratory rate; automated, seated blood pressure; and pulse) are obtained at screening, check-in and follow-up; at 0 hour (predose) on Days 1 and 11; and at approximately 1, 2, 3, 6, and 24 hours after the morning dose on Days 4, 10, and 12. Clinical safety laboratory assessments are performed at screening; on Days −1, 2, 8, and 13; and at follow-up. A serum pregnancy test is obtained at screening and follow-up. A urine pregnancy test is obtained at check-in for each visit for all women. On Day 11, a 12-lead ECG is performed predose, 2 hours postdose, and approximately 24 hours postdose. On other days, 12-lead ECGs is performed only at predose.

Pemigatinib is administered as follows: Participants enter the CRU on Day −1 and remain in the clinic until discharged on Day 13. They receive a single oral dose of pemigatinib 13.5 mg under fasted conditions on Day 1. On Days 4 through 10, they will receive rifampin 600 mg QD under fasted conditions. On Day 11, participants receive single doses of pemigatinib 13.5 mg and rifampin 600 mg under fasted conditions. On Day 12, participants receive rifampin 600 mg QD under fasted conditions. Participants are discharged from the unit on Day 12. Blood samples for PK analysis are collected at 0 hour (predose) and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 16 hours postdose on Day 1; at 24 hours postdose on Day 2; at 48 hours postdose on Day 3; at 72 hours postdose on Day 4; at 0 hour (predose) and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 16 hours postdose on Day 11; at 24 hours postdose on Day 12; and at 48 hours postdose on Day 13.

In both cohorts, each participant undergoes a screening period, a treatment period, and a post-treatment period. During the screening period (up to 28 days), participants sign an informed consent form and are assessed for eligibility. In the treatment period, PK blood samples are collected at scheduled times after each pemigatinib administration to determine plasma concentrations of pemigatinib. The post-treatment period will include a follow-up visit 30+3 days after the final dose of pemigatinib.

Screening lasts up to 28 days. The planned length of treatment is 12 days for Cohort 1 and 13 days for Cohort 2. Follow-up is 30+3 days after the last dose of the study drug. Total duration is up to 66+3 days for Cohort 1 and 69+3 days for Cohort 2.

The key inclusion criteria is male or female healthy adult participants aged 18 to 55 years, with a body mass index between 18 and 32 kg/m^2 inclusive. In addition, the participants should exhibit no clinically significant findings on screening evaluations (e.g., no current or recent history of a clinically significant bacterial, fungal, parasitic, mycobacterial, or viral infection, and not receiving systemic antibiotics). The participants must be willing to avoid pregnancy or fathering children.

The key exclusion criteria include the following:

History or clinical manifestations of significant metabolic, hepatic, renal (eGFR≤90 mL/min/1.73 m2), hematological, pulmonary, cardiovascular, GI, urological, neurological, or psychiatric disorders;

History of clinically significant corneal and retinal disorders;

History of a calcium/phosphate homeostasis disorder and/or extensive ectopic mineralization/calcification;

Serum calcium and phosphorus outside of the institutional normal range;

Current or recent history (<30 days before screening) of a clinically significant bacterial, fungal, parasitic, or mycobacterial infection, or currently receiving systemic antibiotics. Current clinically significant viral infection at screening or check-in;

Clinically meaningful findings on screening assessments (clinical, laboratory, and ECG);

Inability or unwillingness to comply with study procedures;

History of malignancy, with the exception of cured basal cell or squamous cell carcinoma of the skin;

History or presence of an abnormal ECG before dose administration that, in the investigator's opinion, is clinically significant (QTcF interval >450 milliseconds);

Resting pulse <45 bpm or >100 bpm, confirmed by repeat testing at screening;

History of unstable ischemic heart disease or uncontrolled hypertension (blood pressure >140/90 mm Hg at screening, confirmed by repeat testing);

History of stomach, cholecystectomy, or intestinal surgery, except that appendectomy will be allowed;

Presence of a malabsorption syndrome possibly affecting drug absorption (eg, Crohn's disease or chronic pancreatitis);

Use of any tobacco-containing or nicotine-containing products (including cigarette, pipe, cigar, chewing tobacco, nicotine patch, or nicotine gum) within 1-month of screening;

Hemoglobin, white blood cell, or platelet count below the lower reference limit of the testing laboratory at screening or check-in, confirmed by repeat testing. Absolute neutrophil count <laboratory lower limit of normal at screening or check-in, confirmed by repeat testing;

Hepatic transaminases (ALT and AST), alkaline phosphatase, or total bilirubin (except volunteers with Gilbert's disease, for which total bilirubin must be ≤2.0× ULN) >1.25 above the laboratory-defined ULN at screening or check-in, confirmed by repeat testing;

Evidence of hepatitis B virus or hepatitis C virus infection or risk of reactivation or HIV: positive result for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, or positive HIV antibody screening tests;

Current treatment or treatment within 30 days or 5 half-lives (whichever is longer) before the first dose of study medication with another investigational medication or current enrollment in another investigational drug protocol;

Use of any medications (including prescription and over-the-counter) or nonprescription preparations (including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations) within 7 days before study entry, unless deemed acceptable by the investigator;

Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study drug and attending required study visits, pose a significant risk to the participant, or interfere with interpretation of study data; and

Known hypersensitivity or severe reaction to pemigatinib or excipients of pemigatinib.

In Cohort 1, pemigatinib is administered orally as a tablet with a unit dose strength of 4.5 mg and a dosage level of 4.5 mg. Itraconazole is administered orally as a capsule with a unit dose strength of 100 mg and a dosage level of 200 mg.

In Cohort 2, pemigatinib is administered orally as a tablet with a unit dosage strength of 4.5 mg and a dosage level of 13.5 mg. Rifampin is administered orally as a capsule with a unit dose strength of 300 mg and a dosage level of 600 mg.

Plasma concentrations of pemigatinib are quantified by LC-MS. Pemigatinib was assayed with a linear range of 1 nM to 1000 nM. PK parameters of pemigatinib are derived by non-compartmental analysis. The log-transformed PK parameters are compared by treatment using ANOVA. The geometric mean ratios and two-sided 90% confidence intervals of C_{max}, AUC0-t, and $AUC_{0-\infty}$ for pemigatinib are calculated by ANOVA.

Preliminary Results

Of the 36 volunteers enrolled (cohort 1, n=18; cohort 2, n=18), all completed the study. Demographics and baseline characteristics are shown below in Table 3.

TABLE 3

Patient Demographics and Baseline Characteristics

	Clinical Trial (n = 36)	
Characteristic	Cohort 1 (n = 18)	Cohort 2 (n = 18)
Median (range) age, y	34.5 (24-50)	30 (19-49)
Women, n (%)	8 (44)	11 (61)
Race, n (%)		
White	15 (83)	13 (72)
Black	1 (6)	4 (22)
Asian	0	0
American Indian/Alaska Native	0	1 (6)
Other	2 (11)	0

TABLE 3-continued

Patient Demographics and Baseline Characteristics

Characteristic	Clinical Trial (n = 36) Cohort 1 (n = 18)	Cohort 2 (n = 18)
Mean (SD) weight, kg	74.2 (11.2)	73.5 (15.8)
2 Mean (SD) body mass index, kg/m^2	26.8 (3.1)	26.4 (4.0)

FIG. **1** shows the PK of pemigatinib in healthy volunteers after administration of pemigatinib with or without coadministration of itraconazole. Pemigatinib was absorbed quickly with or without itraconazole coadministration (median T_{max}=2.0 h in each case). Pemigatinib plasma concentrations subsequently declined in a biphasic manner. The estimated geometric mean $t_{1/2}$ was significantly shorter for pemigatinib alone versus pemigatinib coadministered with itraconazole (11.8 vs. 18.8 h, respectively; P<0.0001). The C_{max} and $AUC_{0-\infty}$ of pemigatinib increased by 17% and 88%, respectively, upon coadministration with itraconazole; both increases were significant (P<0.0001).

FIG. **2** shows the PK of pemigatinib in healthy volunteers after administration of pemigatinib with or without coadministration of rifampin. Pemigatinib was absorbed quickly with or without rifampin coadministration (median T_{max}=1.5 h vs. 1.0 h for pemigatinib with vs. without rifampin coadministration, respectively). Pemigatinib plasma concentrations subsequently declined in a biphasic manner. The estimated geometric mean $t_{1/2}$ was significantly longer for pemigatinib alone versus pemigatinib coadministered with rifampin (12.7 vs. 4.7 h, respectively; P<0.0001). The C_{max} and AUC_0, of pemigatinib decreased by 62% and 88%, respectively, upon coadministration with rifampin; both decreases were significant (P<0.0001).

Table 4 shows the PK parameters of Cohort 1 and Cohort 2.

Safety and Tolerability

Treatment-emergent adverse events (TEAEs) were reported n 7 (39%) volunteers in Cohort 1 and 6 (33%) volunteers in Cohort 2 with headache reported as the most common TEAE in both cohorts. There were no TEAEs of grade 3 or high, no treatment discontinuations or dose interruptions due to TEAEs, and no serious TEAEs or deaths.

A safety summary of the study is provided in Table 5.

TABLE 5

Safety Summary

	TEAE, n (%) Cohort 1 (n = 18)	Cohort 2 (n = 18)
Any TEAE	7 (38.9)	6 (33.3)
Headache	3 (16.7)	4 (22.2)
Nausea	1 (5.6)	3 (16.7)
Rash papular	2 (11.1)	1 (5.6)
Somnolence	2 (11.1)	1 (5.6)
Dry mouth	2 (11.1)	0 (0)
Dry skin	2 (11.1)	0 (0)
Paraesthesia	0 (0)	2 (11.1)
Vision blurred	2 (11.1)	0 (0)

CONCLUSION

Coadministration of pemigatinib with itraconzole, a potent CYP3A4 inhibitor, resulted in a clinically significant increase in pemigatinib exposure. Coadministration of pemigatinib with rifampin, a potent CYP3A4 inducer, resulted in a clinically significant decrease in pemigatinib exposure. Based on these results, it is recommended that the dose of pemigatinib be reduced by approximately 50% when a

TABLE 4

PK parameters

	PK Parameters C_{max}, nM	T_{max}, h	$t_{1/2}$, h	AUC_{0-t}, nM · h	$AUC_{0-\infty}$, nM · h	CL/F, L/h	Vz/F, L
Cohort 1							
Pemigatinib alone (n = 18)	60.1 ± 25.3 55.2	2.00 (1.00, 4.00)	12.1 ± 2.74 11.8	674 ± 246 634	712 ± 252 672	14.5 ± 4.55 13.7	244 ± 75.8 233
Pemigatinib + itraconazole (n = 18)	68.2 ± 22.1 64.7	2.00 (1.00, 3.00)	19.2 ± 4.30 18.8	1270 ± 381 1210	1320 ± 397 1270	7.63 ± 2.34 7.29	206 ± 63.2 198
P value	0.0098	0.262	<0.0001	<0.0001	<0.0001	<0.0001	0.0001
Geometric mean ratio,* % (90% CI)	117 (107-129)	—	—	191 (177-206)	188 (175-203)	—	—
Cohort 2							
Pemigatinib alone (n = 18)	187 ± 63.3 176	1.50 (0.50, 3.00)	12.9 ± 2.90 12.7	1980 ± 526 1900	2040 ± 556 1960	14.8 ± 4.86 14.1	267 ± 73.1 258
Pemigatinib + rifampin (n = 18)	69.7 ± 20.0 66.9	1.00 (1.00, 3.00)	5.05 ± 2.76 4.69	289 ± 74.9 280	301 ± 75.5 292	97.5 ± 23.8 94.7	673 ± 259 640
P value	<0.0001	0.141	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Geometric mean ratio,* % (90% CI)	38.0 (33.2-43.5)	—	—	14.7 (13.7-15.8)	14.9 (13.9-16.1)	—	—

Values are presented in the format of "Mean ± SD and Geometric Mean except that T_{max} is reported as median (range)

strong CYP3A4 inhibitor is coadministered, and that coadministration of pemigatinib with a strong CYP3A4 inducer should be avoided.

Pemigatinib, when administered alone or in combination with itraconazole or rifampin, was safe and generally well tolerated in this group of healthy male and female volunteers.

Example B. In Vitro Metabolism of Pemigatinib by Individual Recombinant Human Cytochrome P450 Isozymes

In vitro metabolism studies were conducted to determine the human cytochrome P450 (CYP) isozyme(s) capable of metabolizing pemigatinib. Experiments using individual recombinant human CYPs showed that pemigatinib was predominantly metabolized by CYP3A4. In agreement, experiments using human liver microsomes and selective chemical inhibitors of CYPs showed the metabolism of pemigatinib was only inhibited by ketoconazole, a potent CYP3A4 inhibitor. The in vitro metabolism of pemigatinib by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 was negligible. Thus, it is concluded that pemigatinib is predominately metabolized by CYP3A4.

Pemigatinib was incubated with human liver microsomes in the absence and presence of selective chemical inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Pemigatinib (1 μM) was incubated (N=3) with human liver microsomes (1 mg/mL of protein), NADPH (2 mM), and 100 mM potassium phosphate buffer (pH 7.4) at 37° C. Parallel incubations using the same conditions included either furafylline (10 μM), ticlopidine (2 M), quercetin (10 μM), sulfaphenazole (10 μM), tranylcypromine (20 μM), quinidine (1 μM), or ketoconazole (1 μM) to selectively inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A, respectively (Walsky and Obach 2004, Walsky et al 2006, Khojasteh et al 2011). Aliquots were taken at 0, 10, 20, and 30 minutes and denatured with methanol. After centrifugation to remove the denatured proteins, the resulting supernatants were analyzed by LC/MS.

To measure pemigatinib levels from in vitro incubations, samples were injected onto an Agilent Zorbax 5 μm SB-C18 column (2.1×50 mm) coupled to a ThermoFinnigan LCQ Fleet Ion-Trap mass spectrometer (Thermo-Fisher Scientific, Waltham, Mass.) operated in positive ionization mode. The mass spectrometer was coupled to a Shimadzu Sil HT-C combined autosampler/controller combined with a Shimadzu LC-10A binary gradient pump system (Shimadzu Scientific Instruments, Columbia, Md.). The chromatographic separation was achieved using a gradient elution consisting of mobile phase A: 5 mM ammonium formate in deionized water (Millipore Inc., Billerica, Mass.) that had been pH adjusted to pH 3.4 with formic acid (approximately 0.1%), and mobile phase B: 100% methanol (recombinant isozyme study) or 100% acetonitrile (chemical inhibitor study).

In vitro metabolism studies were conducted to determine the individual human recombinant CYP isozymes capable of metabolizing pemigatinib (1 μM) and included CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. The percent of pemigatinib remaining after a 30-minute incubation with individual CYPs is shown in Table 6. Of the CYP isozymes evaluated, pemigatinib was metabolized to the greatest extent by CYP3A4. The metabolism of pemigatinib by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, was negligible.

TABLE 6

The In Vitro Metabolism of Pemigatinib by Individual Human Recombinant CYP Isozymes

CYP Isozyme	Average Percent (N = 2) of Pemigatinib Remaining vs Control (30 mins)
CYP1A2	92
CYP2B6	96
CYP2C8	94
CYP2C9	88
CYP2C19	95
CYP2D6	94
CYP3A4	14

To determine the relative contributions of CYP isozymes to the metabolism of pemigatinib in the liver, this compound was incubated in triplicate with human liver microsomes and selective chemical inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

When pemigatinib was incubated with human liver microsomes in the absence of chemical inhibitors, 72% of parent remained after 30 minutes, but when co-incubated with ketoconazole (2 M), a selective inhibitor of CYP3A4, the metabolism of pemigatinib was inhibited (97% of the parent compound remained). Other selective inhibitors had marginal effects on the metabolism of pemigatinib; therefore these data are supportive of the conclusion that pemigatinib is predominantly metabolized by CYP3A4.

TABLE 7

Effects of Chemical Inhibitors on the Matebolism of Pemigatinib in Human Liver Microsomes.

Chemical Inhibitor	Concentration (μM)	Inhibitor of Isozyme	Mean Percent of Pemigatinib Remaining After 30-Minute Incubation (N = 3)
Pemigatinib (1 μM)		No Inhibitor	72 ± 1
Furafylline	10	CYP1A2	67 ± 1
Ticlopidine	2	CYP2B6	67 ± 3
Quercetin	10	CYP2C8	77 ± 1
Sulfaphenazole	10	CYP2C9	70 ± 3
Tranylcypromine	20	CYP2C19	73 ± 2
Quinidine	1	CYP2D6	71 ± 1
Ketoconazole	2	CYP3A4	97 ± 2

Example C. Model Development for Pemigatinib and Evaluation of Drug-Drug Interactions

A minimal physiologically based pharmacokinetic (PBPK) with advanced dissolution absorption and metabolism (ADAM) absorption model for pemigatinib that incorporates CYP3A4-mediated metabolism derived from in vitro data, mass balance data, and clinical PK data (Example A) was developed. Data from in vitro studies have indicated that CYP3A4 is the major isozyme responsible for the metabolism of pemigatinib (Example B). Based on mass balance and metabolite identification data, the oral absorption of pemigatinib is nearly complete and renal excretion is low (~1.0%), and liver metabolism is inferred to be the major clearance pathway for pemigatinib.

PBPK models that have been validated with clinical pharmacokinetic and DDI data can be used to predict other unknown DDI scenarios. The simulation results can also be used to support dose adjustment and label statements. The aims of this modeling and simulation study were to develop

a PBPK model for pemigatinib, using in silico, in vitro, and clinical data to predict the drug-drug interaction.

Model Development

The initial PBPK model for pemigatinib was built using in vitro and in silico data. Data from in vitro studies (Example B) have indicated that CYP3A4 is the major isozyme responsible for the metabolism of pemigatinib. Based on mass balance and metabolite identification data, the oral absorption of pemigatinib is nearly complete (1.3% of the administered radioactive dose was recovered as unchanged pemigatinib in feces) and renal excreation is low (~1.0% of the dose is excreted in urine as unchanged pemigatinib), and liver metabolism is inferred to be the major clearance pathway for pemigatinib. Therefore, a minimal PBPK with ADAM absorption model for pemigatinib that incorporates CYP3A4-mediated metabolism derived from in vitro data and human ADME data was then further developed and model was used to describe the clinical PK data from pemigatinib alone cohorts in Example A. The sensitivity analysis of pemigatinib $f_{mCYP3\ A4}$ on drug interaction with itraconazole suggested that CYP3A4 contributes~55% of the metabolic clearance for pemigatinib. The verified pemigatinib model was then used to simulate the observed effect of itraconazole on pemigatib pharmacokinetics, and to confirm the contribution of CYP3A4 ($f_{mCYP3\ A4}$) to pemigatinib metabolic clearance. Finally, the pemigatinib PBPK model was applied to simulate the effect of other inhibitors and inducers on pemigatinib pharmacokinetics.

Simulations were performed using pemigatinib PBPK model and compared with the observations in the clinical studies available. The pemigatinib PBPK model was validated by simulation of DDIs between pemigatinib and itraconazole or rifampin using a Simcyp virtual population, with the study design matching the corresponding clinical DDI study in healthy volunteers. The itraconazole capsule (200 mg) was administered daily from Day 1 to Day 6 and a single 4.5-mg dose of pemigatinib tablet was administered orally with itraconazole on Day 5. The rifampin capsule (600 mg) was administered daily from Day 1 to Day 8 and a single 13.5-mg dose of pemigatinib tablet was administered orally with rifampin on Day 8. The simulations were performed using an age range of 18-55 years (proportion of female volunteers: 0.5).

The verified Pemigatinib PBPK model was used to predict the effect of other strong (clarithromycin), moderate (diltiazem, erythromycin, and cyclosporine), and mild (fluvoxamine) CYP3A4 inhibitors and moderate (efavirenz) and mild (dexamethasone) CYP3A4 inducers on pemigatinib PK. The Simcyp default PBPK models for clarithromycin, erythromycin, diltiazem, cyclosporine, fluvoxamine, and efavirenz were used in these simulations. Dexamethasone PBPK models are not available in the Simcyp model library. Therefore, a literature reported dexamethasone PBPK model was used for simulation. For CYP3A4-mediated inhibition/induction simulation, the inhibitors/inducers were administered daily from Day 1 to Day 12 and a single 13.5-mg dose of pemigatinib tablet was administered orally on Day 8. The simulations were performed using an age range of 18-55 years (proportion of female volunteers: 0.5).

Results

A minimal PBPK with ADAM absorption model for pemigatinib that incorporates CYP3A4-mediated metabolism derived from in vitro data and in vivo clinical data was developed. FIG. **3** shows the observed and simulated mean plasma concentration-time profiles for pemigatinib following a single oral dose of 4.5 mg (FIG. **3**A) and 13.5 (FIG. **3**B) mg pemigatinib tablet alone. Predicted and observed geometric mean plasma C_{max} and $AUC_{0-\infty}$ values for pemigatinib tablets are shown in Table 8. The simulated profiles of pemigatinib are comparable to the clinical data and the predicted geometric mean C_{max} and $AUC_{0-\infty}$ values are within 0.93- to 1.11-fold of the observed data.

TABLE 8

Predicted and Observed Exposures (Geometric Mean) Following a Single Oral Dose of 4.5 mg or 13.5 mg Pemigatinib Tablets

Dose	Predicted C_{max} (nM)	Observed C_{max} (nM)	Predicted AUC (h * nM)	Observed AUC (h * nM)	C_{max} (pred/obs)	AUC (pred/obs)
4.5 mg	52.6	55.2	627	672	0.95	0.93
13.5 mg	176	158	1878	I960	111	0.95

The pemigatinib PBPK model was developed from healthy volunteer was used to describe cancer patients PK data from phase I dose escalation and dose expansion study (6-20 mg). The model was used to predict pemigatinib plasma concentration-time curves in cancer patients after multiple oral dose of 6, 9, 13.5 and 20 mg pemigatinib because only one patient was dosed for 1, 2 and 4 mg, respectively. FIG. **4** shows the observed (circles) and simulated (lines) mean plasma concentration-time profiles for pemigatinib following a multiple oral dose administration. Predicted and observed geometric mean plasma C_{max} and AUC values for pemigatinib tablets are shown in Table 9. The simulated PK profiles of pemigatinib are comparable to the clinical data and the predicted geometric mean C_{max} and AUC values are within 0.676- to 1.18-fold of the observed data.

TABLE 9

Predicted and Observed Exposures (Geometric Mean) Following a Multiple Dose of Pemigatinib Tablets

Dose	Predicted Cmax, ss (nM)	Observed Cmax, ss (nM)	Predicted AUCss (h * nM)	Observed AUCss (h * nM)	Cmax, ss (pred/obs)	AUCss (pred/obs)
6 mg	77.4	101	1002	1110	0.766	0.902
9 mg	116	161	1259	1508	0.720	0.834
13.5 mg	193	175	3073	2600	1.10	1.18
20 mg	257	380	3345	4180	0.676	0.800

The sensitivity analysis of pemigatinib $f_{mCYP3\ A4}$ on drug interaction with itraconazole were used to determine CYP3A4 contribution of metabolic clearance for pemigatinib. The input of CYP3A4 CL_{int} was varied to obtain a range of f_{mCYP3A} from 0.25 to 0.95 (using the Simcyp retrograde calculator). The simulations of itraconazole-

pemigatinib DDIs with different f_{mCYP3A} values for pemigatinib were compared with the observed DDI data. When $f_{mCYP3\ A4}$ was assigned to be 55%, the best prediction was achieved by PBPK model for the effect of DDI between pemigatinib and itraconazole (FIG. **5** and Table 10).

TABLE 10

Simulated Pemigatinib Geometric Mean C_{max} and AUC Ratios using PBPK Model with Various $f_{mCYP3A4}$ Values

	C_{max} Ratio		AUC Ratio	
$f_{mCYP3A4}$ (%)	Predicted	Observed	Predicted	Observed
25	1.09	1.17	1.31	1.88
55	1.22		1.98	
75	1.32		2.88	
95	1.44		5.02	

The comparison between simulated and observed pemigatinib PK in the presence and absence of itaconazole or rifampin are presented in FIG. **6** and FIG. **7**, respectively. The predicted and observed geometric mean plasma C_{max} and AUC values for pemigatinib tablets are shown in Table 11.

TABLE 11

Predicted and Observed Pemigatinib C_{max} and AUC Ratios Following a Single Oral Dose of Pemigatinib Tablets With and Without Itraconazole or Rifampin Administration

CYP3A4	C_{max} Ratio		AUC Ratio	
Perpetrator	Predicted	Observed	Predicted	Observed
Itraconazole	1.22 (1.20, 1.24)	1.17 (1.07, 1.29)	1.98 (1.91, 2.05)	1.88 (1.75, 2.03)
Rifampin	0.604 (0.572, 0.638)	0.380 (0.332, 0.425)	0.323 (0.299, 0.349)	0.149 (0.139, 0.161)

Values are presented in the format of geometric mean (90% confidence intervals)

The model-predicted pemigatinib AUC ratio of 1.98 (90% CI:1.91, 2.05) and C_{max} ratio of 1.22 (90% CI:1.20, 1.24) are similar to the observed AUC ratio of 1.88 (90% CI:1.75, 2.03) and C_{max} ratio of 1.17 (90% CI:1.07, 1.29) for itraconazole DDI. The predicted geometric mean AUC ratios and C_{max} ratios are within the 90% CI of the observed data.

However, underprediction is observed for rifampin DDI. Model-predicted pemigatinib AUC ratio of 0.323 (90% CI:0.299, 0.349) and C_{max} ratio of 0.604 (90% CI:0.572, 0.638) are approximately 1.5 to 2-fold higher comparing to the observed AUC ratio of 0.149 (90% CI:0.139, 0.161) and C_{max} ratio of 0.380 (90% CI:0.332, 0.425) for rifampin DDI. In Example A, the observation of an 85% reduction in AUC and 63% decrease in half-life of pemigatinib following rifampin coadministration. In addition, the first pass gut and liver metabolism is expected to be low due to high permeability and low oral clearance of pemigatinib. All of these suggest that a decrease in bioavailability of pemigatinib occurred with rifampin coadministration, in addition to an increase in systemic clearance (eg, reduced absorption).

The final pemigatinib PBPK model was not able to accurately predict drug-drug interaction between pemigatinib and rifampin which could be due to additional DDI effect on absorption of pemigatinib. The model with 55% $f_{mCYP3\ A4}$ was used to predict DDI effect on pemigatinib PK when co-administration with moderate and mild CYP3A4 inducers. Results of the simulated effect of strong, moderate, and mild CYP3A inhibitors/inducers on pemigatinib pharmacokinetics are summarized in Table 12 and illustrated in FIG. **8**.

TABLE 12

Simulated Pemigatinib Drug-Drug Interactions With Various CYP3A4 Inhibitors or Inducers

CYP3A4 Perpetrators and Dose Regimen	Inhibition/Induction Mechanism	AUC Ratio	C_{max} Ratio
Itraconazole 200 mg QD	Strong, reversible inhibition	1.98 (1.91, 2.05)	1.22 (1.20, 1.24)
Clarithromycin 500 mg BID	Strong, time dependent inhibition	1.89 (1.80, 1.98)	1.20 (1.18, 1.21)
Erythromycin 500 mg BID	Moderate, time dependent inhibition	1.66 (1.59, 1.73)	1.16 (1.14, 1.17)
Diltiazem 60 mg TID	Moderate, time dependent inhibition	1.51 (1.46, 1.56)	1.13 (1.12, 1.14)

TABLE 12-continued

Simulated Pemigatinib Drug-Drug Interactions With Various CYP3A4 Inhibitors or Inducers

CYP3A4 Perpetrators and Dose Regimen	Inhibition/Induction Mechanism	AUC Ratio	C_{max} Ratio
Fluvoxamine 50 mg QD	Mild, reversible inhibition	1.082 (1.075, 1.089)	1.048 (1.044, 1.053)
Rifampin 600 mg QD	Strong, inducer	0.323 (0.299, 0.349)	0.604 (0.572, 0.638)
Efavirenz 600 mg QD	Moderate, inducer	0.482 (0.455, 0.512)	0.758 (0.736, 0.781)
Dexamethasone 8 mg QD	Mild, inducer	0.995 (0.994, 0.996)	0.996 (0.996, 0.997)

Values are presented in the format of geometric mean (90% confidence intervals).

The simulated DDI results for co-administration with various CYP3A4 inhibitors or inducers were used for pemigatinib dose recommendation. The model-simulated pemigatinib geometric mean C_{max} and AUC ratios are 1.20 and 1.89, 1.16 and 1.66, 1.13 and 1.51, 1.05 and 1.08, 0.758 and 0.482, and 1.00 and 1.00, respectively, when coadministration with strong inhibitors clarithromycin, moderate inhibitors erythromycin and diltiazem, a mild inhibitor fluvoxamine, a moderate inducer efavirenz and a mild inducer dexamethasone. The recommendation based on this simulation and clinical DDI result is to reduce pemigatinib dose by approximately 50% for coadministration with strong CYP3A4 inhibitors. For coadministration with moderate CYP3A4 inhibitors, the model-simulated pemigatinib AUCs are increased by approximately 50% and it is covered by safety margin. Therefore, no dose adjustment is required with coadministration of pemigatinib and moderate and mild CYP3A4 inhibitors. The simulation and clinical DDI result also suggest that co-administration of a strong and moderate CYP3A4 inducers should be avoided due to larger than 50% of pemigatinib AUC decrease and no dose adjustment is required with coadministration of pemigatinib and mild CYP3A4 inducers. with clinical data. The estimated $f_{mCYP3A4}$ (55%) for pemigatinib was verified using the observed clinical DDI study with itraconazole.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

What is claimed is:

1. A method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of a CYP3A4 perpetrator.

2. A method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of a strong CYP3A4 inhibitor.

3. The method of claim **1**, A method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of a moderate to strong CYP3A4 inducer.

4. A method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of itraconazole.

5. A method of treating cancer comprising administering a therapy to a patient in need thereof, wherein the therapy comprises administering a therapeutically effective amount of pemigatinib to the patient while avoiding the concomitant administration of rifampin.

6. The method of claim **1**, wherein the cancer is bladder cancer, breast cancer, cervical cancer, cancer of the small intestine, colorectal cancer, endometrial cancer, gastric cancer, head and neck cancer, kidney cancer, liver cancer, lung cancer, ovarian cancer, prostate cancer, testicular cancer, uterine cancer, vulvar cancer, esophageal cancer, gall bladder cancer, pancreatic cancer, thyroid cancer, skin cancer, brain cancer, leukemia, multiple myeloma, chronic lymphocytic lymphoma, adult T cell leukemia, B-cell lymphoma, acute myelogenous leukemia, Hodgkin's or non-Hodgkin's lymphoma, Waldenstrom's Macroglubulinemia, myeloproliferative neoplasms, chronic myelogenic lymphoma, acute lymphoblastic lymphoma, hairy cell lymphoma, Burkett's lymphoma, glioblastoma, melanoma, rhabdosarcoma, lymphosarcoma, osteosarcoma, solid tumor, cholangiocellular carcinoma, and myeloid/lymphoid neoplasms.

7. The method of claim **6**, wherein the myeloid/lymphoid neoplasm is 8p11 myeloproliferative syndrome.

8. The method of claim **6**, wherein the cancer is cholangiocellular carcinoma.

9. The method of claim **6**, wherein the cancer is bladder cancer.

10. The method of claim **1**, wherein the administration of pemigatinib comprises:

(a) a continuous daily administration of an intended amount or adjusted amount of pemigatinib to the patient in need thereof; or

(b) a 21-day dosing cycle comprising:14 days of daily administration of an intended amount or adjusted amount of pemigatinib to the patient in need thereof and 7 days without administration of pemigatinib.

11. The method of claim **1**, wherein the cancer is liver cancer.

* * * * *